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THE CHEMICAL ASPECTS OF CANCER[1]

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Any lecture on the chemical aspects of cancer should, at the outset, include a tribute to Percival Pott (1), to whom is due the credit of being the first man to describe cancer as an industrial disease due to exposure to tar. In 1775 Pott, in his "Chirurgical Observations," described chimney sweeps' cancer in a most detailed and comprehensive communication. The description is so complete that it leaves no room for doubt that cancer was the disorder encountered, and that the author recognized clearly that exposure of the skin to tar was the etiologic factor. It is interesting to note that 140 years passed before this observation was extended by the application of the experimental method to the principle which Pott disclosed.

In 1912 Yamagiwa and Ichikawa (2), convinced of the etiologic rôle of tar, applied this material to the ears of rabbits and succeeded in producing cancer at the site of the application. Once the rôle of tar in the production of cancer had been established experimentally, the ground was broken for the basic studies of the biochemists, notably Cook, Kennaway and their associates (3, 4), who isolated in pure form certain constituents of tar which are cancer-producing when allowed to come in contact with the tissues of the mouse. These constituents have in common a structure composed of multiple benzene molecules linked together. The benzene is composed of 6 carbon atoms arranged in the form of a ring, and so the carcinogenic chemicals are made up of groups of these rings fused together. Substances of this type are known in general as polynuclear aromatic hydrocarbons.

The isolation of pure carcinogenic chemicals led to two sets of experiments which, although their significance was not understood at the time, have a direct and important bearing on the current line of investigation.

1. Cook, in an attempt to investigate more minutely the chemical structure of the cancer-producing compounds, began altering them synthetically and testing the carcinogenic effects of the altered compounds upon animals. In the course of these studies Cook (4) and also Fieser (15) showed that certain hydroxy derivatives, formed by the simple addition of an OH group to the carcinogen, were without power to induce disease. This addition, or hydroxylation, involves an oxidative change. On the basis of this observation, Cook suggested further experiments to determine to what extent this phenomenon was due to the position of the hydroxyl group. With these experiments this lecture is not concerned, but it is important to note that so far no synthetic hydroxy derivative of one of the recognized carcinogens has been shown clearly to possess the power to produce cancer.

[1] Delivered as part of A Series of Lectures on Steroid Hormones at the Blumenthal Auditorium of The Mount Sinai Hospital, New York, May 12, 1941.

2. At about the time that Cook was studying the effect of synthetic hydroxylation, Boyland (5) published the results of a study of the form in which animals excreted orally administered dibenzanthracene. He reported that he could recover from the excreta of animals to which dibenzanthracene had been fed a phenolic, or hydroxylated, derivative. Furthermore, he isolated this derivative in its crystalline form, and ascertained its melting point, but did not determine the positions of the hydroxyl groups. Curiously enough, he does not appear to have noted the implication of this observation as suggested by the known fact that synthetic hydroxylated derivatives are in general innocuous.

At the time the reports of Cook and Boyland appeared, a study was in progress, at the Hospital of the Rockefeller Institute, of the possible etiology of aplastic anemia and leukemia. There was good evidence that these disorders, in both men and animals, followed exposure to certain aromatic hydrocarbons, similar in structure to the known carcinogens and to the sex hormones. Hence it seemed essential to ascertain how the body metabolized these compounds. This information was felt to be particularly necessary because, while in some instances the patients had been exposed to unusually large amounts of the compounds, in other cases the amounts were so small that their etiologic rôle can only be accounted for by a hypersusceptibility of the patient to the aromatic hydrocarbons. Clearly, such a hypersusceptibility must depend upon some abnormality in the manner in which these potentially toxic chemicals are metabolized in the body of the susceptible individual.

Perusal of the literature suggested that the key to this metabolic abnormality might lie in the results of the two sets of experiments discussed above. If it could be shown that the conversion by the animal of dibenzanthracene to a hydroxylated derivative was the conversion of a carcinogenic to a non-carcinogenic compound, it might be possible to ascertain upon what chemical system this conversion depends. Moreover, by making more of this system available, the ability of the animal to effect the conversion might well be increased.

At the time this concept was developed, no adequate methods were at hand by which the ability of man or animals to metabolize cyclic hydrocarbons by the ring oxidation could be measured. Accordingly it became necessary to develop and apply several new techniques. Since the amounts of material to be studied were exceedingly small, chemical methods involving isolation were inadequate. By the use of the spectroscope, however, minute amounts of a given substance can be identified by the characteristic absorption of different wave lengths of light which the substance causes under the proper conditions. This method, therefore, seemed the most likely to yield satisfactory results, and accordingly it was adopted by Dr. Dobriner (6, 16) who further developed it in the course of his work. He found that by simple fractionation of excreta into solutions in which compounds of similar chemical structure were grouped together, a solution could be obtained which contained relatively few of the desired constituents—so few that identification by absorption spectroscopy could be made. Furthermore, he found that by the application of molecular distillation and chromatographic absorption, members of a group of compounds which gave overlapping absorption bands could be separated from each other.

The new methods were then applied to a study of the conversion by animals of dibenzanthracene, since that compound proved to have a peculiarly characteristic absorption spectrum. In the illustration (fig. 1) the spectrum of pure dibenzanthracene is shown in a series of dilutions sufficient to bring out the

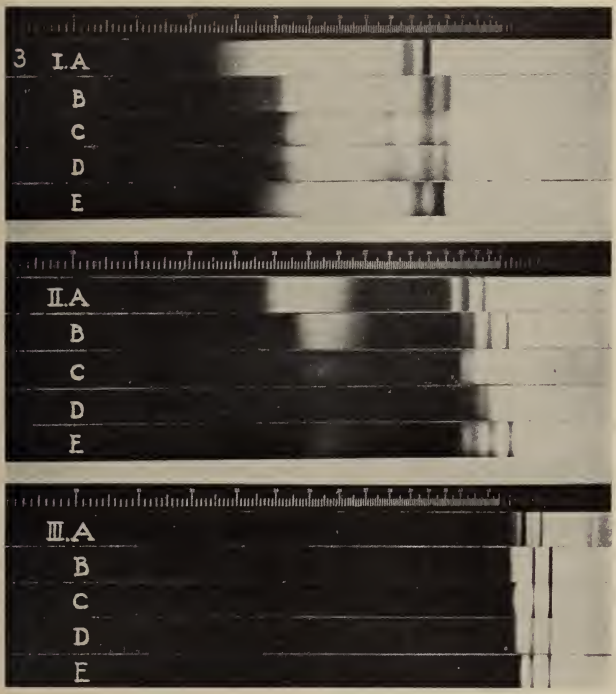

FIG. 1. Comparison of the absorption bands given by: (A)-1,2,5,6-Dibenzanthracene (B)-4′,8′-Dihydroxydibenzanthracene synthesized by Fieser and Cason. (C)-Dihydroxydibenzanthracene excreted by rats after the injection of 1,2,5,6-dibenzanthracene. (D)-Dihydroxydibenzanthracene excreted by mice after the injection of 1,2,5,6-dibenzanthracene. (E)-Dihydroxydibenzanthracene excreted by rabbits after the injection of 1,2,5,6-dibenzanthracene.

complete set of band structures. When rabbits were injected with this pure substance and their excreta fractionated and examined spectroscopically, absorption bands were found which were basically different from those given by the injected dibenzanthracene, but which resembled them sufficiently to suggest

that a new compound had been formed by the animal from the substance administered. Since the new compound was phenolic in nature it was naturally supposed that it might be the dihydroxydibenzanthracene described by Boyland. The truth of this supposition was established by a long series of experiments, in the course of which 50 mg. of the hydroxy substance were isolated, crystallized and compared spectroscopically with the absorption curve of Boyland's hydroxy compound sent us from England. The two sets of curves were practically identical, clear proof that they were produced by the same chemical substance. Further proof was afforded by the fact that the melting point of Boyland's material was the same as that of ours.

We had isolated, then, from rabbits, a naturally formed dihydroxydibenzanthracene, and we had accumulated sufficient material to test its carcinogenic power, an experiment which Boyland had been unable to make. Accordingly, each of 12 mice of a strain highly susceptible to the carcinogenic effect of dibenzanthracene was injected subcutaneously with 4 mg. of rabbit dihydroxydibenzanthracene in lard. Littermate controls each received 4 mg. of pure dibenzanthracene in the same solvent. The results of this test were striking: All of the first group of animals developed malignant tumors at the site of injection, and none of the animals given the dihydroxydibenzanthracene did so (6). It was clear that the hydroxylated derivative formed by rabbits was without carcinogenic power in the mouse, as far as the limited number of observations could establish this point. This fact is of especial importance since the rabbit is very resistant to the carcinogenic effect of dibenzanthracene or compounds similar to it.

Further studies (6, 16) showed that the derivative of dibenzanthracene excreted by the rat and mouse, while also a hydroxy compound, differed somewhat from the derivative excreted by the rabbit. The derivative in the mouse and rat excreta, however, was obtainable in such small amounts that it was extremely difficult to isolate enough for a test of its cancer-producing power. Dr. Fieser (14) came to our assistance, and undertook to synthesize a series of hydroxylated derivatives of dibenzanthracene in the hope of obtaining one which would be identical with that excreted either by the rabbit or by the rat and mouse. By great good fortune the first compound synthesized was, spectroscopically and by melting point, identical with the rat-mouse derivative. It was a 4′8′-dihydroxy compound, and has been tested for its carcinogenic power by Dunlap and Warren. It was found to be inactive (7).

Similar studies, of the metabolism of other aromatic hydrocarbons were made, and the results of all of them indicate that the hydroxylation, or ring oxidation, is a standard method by which the body alters the simple ring structure. Our evidence suggests, we believe, that the oxidation of a carcinogenic aromatic ring compound, such as dibenzanthracene, to an innocuous derivative is a protective conversion.

It was next desirable to establish what enzyme or chemical system brings about this conversion. Obviously, if such a system could be identified, isolated, and administered in effective form, it might be useful in inhibiting or pre-

venting altogether the carcinogenic effect by increasing the ability of the animal to convert a carcinogen to a non-carcinogen. What sort of an enzyme might it be? Clearly, since the seemingly protective conversion is an oxidative one, the enzyme which causes it might be one of those already proved to effect oxidation. The classic experiments of the German and Scandinavian schools prove that the vitamins nicotinic acid and riboflavin act as essential parts of oxidative enzyme systems. It was logical, then, to attempt to establish whether these vitamins or the enzymes of which they form essential parts are concerned in the protective, oxidative conversion of carcinogens to non-carcinogenic substances.

We had, originally, high hopes of being able to establish this point by our spectroscopic studies of the conversion of dibenzanthracene by animals depleted of flavin and nicotinic acid. The compound is so high in potency, however, that the demonstration of an effect of diet on susceptibility to it would be difficult. Moreover, we are still not satisfied that our spectroscopic methods are sufficiently accurate, in a quantitative sense, to provide us with acceptable data. By great good luck, however, at about this point in the development of our study the Japanese workers, led by Kinosita (8), published experimental results which provided us with exactly the needed conditions.

Kinosita showed that cancer of the liver occurred regularly in rats fed a basal diet composed of brown rice and carrot, to which was added 3 per cent of an olive oil solution of butter yellow, or dimethylaminoazobenzene. It should be noted that this compound, like those previously discussed, also contains the benzene nucleus. If to this diet certain supplements such as yeast or liver were added, the animals were completely protected against the carcinogenic effects. Both yeast and liver were known to be excellent sources of riboflavin and of nicotinic acid; hence it was not impossible that the protective effect of these dietary substances was due to their content of one or both of these vitamins acting as essential parts of oxidizing enzyme systems.

We attempted to ascertain the facts regarding this point. It was first necessary to repeat in detail and on a large scale the experiments of the Japanese workers. This has been done. In our hands the feeding of butter yellow to rats of three different strains taking a basal diet of brown rice and carrot results in the production of liver cancer in nearly every animal at the end of 150 days (9). The location of the cancer in the liver is due presumably to the fact that the butter yellow is transported from the intestinal tract to the liver, where it is broken down. If the basal diet, with butter yellow, is supplemented with 15 per cent of yeast or 5 per cent of liver extract powder, Lilly 343, absolutely no injurious effect is shown in the livers of the animals at 150 days after the beginning of treatment. If amounts of yeast or liver extract smaller than those mentioned are fed, incomplete protection is observed. Furthermore, the degree of protection provided by the yeast and liver extract is directly proportional to the amounts of those substances in the diet. We already knew that the yeast and also the liver extract used were rich in their content of both nicotinic acid and riboflavin as well as other vitamins, and we were aware, furthermore, that those particular vitamins were essential for the activity of the oxidizing

enzymes, Coenzyme I and flavoprotein, respectively. It was clearly necessary to ascertain whether the vitamins were lacking from the basal diets fed, and if so whether supplement of the diets with them would result in protection.

Riboflavin was first studied. We knew that 20 gamma of this substance per animal per day is the normal requirement for rats, and the diet probably provided somewhat less than this amount. Hence, a riboflavin deficiency was probably caused by the basal diet feeding. However, this point required further confirmation, and accordingly the output of riboflavin in the urine of several groups of rats receiving, respectively, a normal diet, the basal diet which brought out the carcinogenic effect of butter yellow, the basal diet plus butter yellow, and the basal diet plus butter yellow plus the protective supplement, were studied (10). The results were striking. Whereas rats on a normal diet excreted 18 gamma of riboflavin daily, the animals receiving the basal diet, alone or supplemented with butter yellow, excreted less than 2 gamma daily. Rats taking the basal diet, butter yellow and protective yeast supplement, excreted nearly a normal amount, or 15.8 gamma daily. The results of this study indicate clearly that the diet used, which renders the animal susceptible to cancer, is riboflavin-deficient.

Further confirmation of the riboflavin deficiency was supplied by the measurement of the riboflavin content of the livers of the animals in the various groups just mentioned. The livers of the rats on a normal diet contained well over 150 gamma of riboflavin per gram of dry weight, whereas those of the animals taking the basal diet without butter yellow contained 80 gamma per gram. When butter yellow was added to this basal diet, the liver content dropped to under 50 gamma. When effective supplements were added to the diet, however, such as whole yeast or its extracts, normal values of 150 gamma were present.

Clearly, from these studies it was necessary to explore the possibility that riboflavin was the protective agent. Animals fed the basal diet with added butter yellow regularly developed liver cancer, as previously stated. If this regimen was supplemented by nicotinic acid or by vitamin-free casein, no protection was observed. When 5 mg. daily of riboflavin was added, there seemed to be only a slight protective effect, but when to this diet nicotinic acid was added the effect was somewhat more pronounced and nearly 50 per cent protection was obtained. This figure was reduced to under 20 per cent if the amount of riboflavin fed as supplement was reduced. If the basal diet containing butter yellow was supplemented with riboflavin and casein together, however, almost 90 per cent protection resulted (11). The results of these experiments allow of only one interpretation: that at least two factors are required for protection. One of these appears to be riboflavin, and another seems to be provided by casein. Further experiments are in progress to establish what constituent of casein is responsible for this effect.

These somewhat involved experiments may be summarized as follows:

1. Rats taking the basal diet which renders them susceptible to the carcinogenic effect of butter yellow as well as rats fed the diet plus butter yellow, show low urinary and hepatic riboflavin levels.

2. High urinary and hepatic riboflavin levels are found in animals which have received protective supplements of yeast.

3. Riboflavin protects against cancer to a slight extent when fed alone, and to a greater extent when fed with nicotinic acid. When given in conjunction with casein, riboflavin seems to be nearly totally protective at 150 days.

Whereas further confirmation of these results is required and experiments are in progress, the results so far are highly suggestive.

The next vitamin to study was nicotinic acid, even though alone it had been shown to have no protective effect against butter yellow. Here a different problem was presented, for, while we had a good method for the measurement of riboflavin as such, we were not satisfied with our methods for measuring nicotinic acid. It should be recalled here that these vitamins act as essential parts (prosthetic groups) of oxidative enzymes. As previously stated, nicotinic acid is a vital part of cozymase, or Coenzyme I; hence by measuring the Coenzyme I activity of tissues one can ascertain the presence of nicotinic acid, in its functional form, in those tissues. Dr. Dexter, in my laboratory, developed a satisfactory procedure for measuring the activity of this enzyme by the amount of CO_2 given off in a standard system in a Barcroft-Warburg respirometer in which the unknown served as the source of Coenzyme I.

This sort of enzyme measurement was to be preferred to simple estimation only of the essential component, since we know that the rat can form nicotinic acid and does not need that compound as a supplement to the diet. Furthermore, we had proved that nicotinic acid was without protective power against the carcinogenic effects of butter yellow. It was not impossible, however, that some metabolite of butter yellow might damage the enzyme system of which nicotinic acid forms an essential part and so set up a deficiency of the nicotinic acid coenzyme even though ample nicotinic acid were present.

When the procedure had been standardized, the livers of the various groups of animals were examined for their content of the coenzyme which contained the nicotinic acid. The livers of the animals taking the normal diet or the basal diet showed normal Coenzyme I content, which is just under 500 gamma per gram of fresh tissue, and this was also true of the animals taking the basal diet plus butter yellow and protective supplement. The livers, and also the tumor tissue, of animals taking the basal diet plus butter yellow, however, showed very low values (10).

How are these results to be interpreted? The normal Coenzyme I activity of the basal diet rat liver is completely in accord with the evidence that nicotinic acid is not a required dietary component for the rat, since the rat can synthesize that compound. Butter yellow feeding, clearly, results in an inhibitory effect on the Coenzyme I system which is certainly not due to a lack of nicotinic acid because the rat can synthesize that compound as needed, and supplement of the diet with nicotinic acid does not prevent the effect. The only explanation we can provide for the phenomenon just described is that probably riboflavin lack interferes in some way with the normal mechanism of the body which protects against the carcinogenic effect of butter yellow, and due to this inter-

ference an abnormal metabolite of butter yellow is formed which prevents synthesis of Coenzyme I. The fact is also worthy of note that cancer formation in these experiments parallels the lack or inhibition of a Coenzyme I system.

Once the conclusion just mentioned had been arrived at, it was clearly necessary to establish how the carcinogenic butter yellow is metabolized in the animal body and what constituent of it may, if improperly detoxified, poison the Coenzyme I system. Kinosita had suggested that butter yellow is broken down by a separation of its two rings at their linkage, one ring going to dimethylparaphenylenediamine and the second ring through aniline to aminophenol. Careful studies in my laboratory with actual isolation of the metabolites in the excreta and establishment of their structures by combustions and by melting point determinations did not support the hypothesis of Kinosita (12). We have been able to isolate only two basic derivatives, paraphenylenediamine and aminophenol. Small amounts of each of these compounds were isolated in the free form, but the greater part of both were present as the acetylated derivatives. Aniline and dimethyl-paraphenylenediamine have not been isolated from the urines of the rats, but both of them may be possible intermediates.

Our studies gave us, then, seven compounds of which the effect on the Coenzyme I system could be tested. These tests were made in the Warburg apparatus. Butter yellow, aniline and aminophenol were practically without effect. Dimethylparaphenylenediamine and paraphenylenediamine inhibited the Coenzyme I system completely in concentrations of 1×10^{-4} M and 2×10^{-4} M respectively. Furthermore, experiment proved beyond question that the acetylated derivatives of both paraphenylenediamine and dimethylparaphenylenediamine were completely without this inhibitory effect on the system (13). Acetylation, then, is a protective conversion operative in the case of the toxic breakdown product of butter yellow, be it either the dimethyl- or the simple paraphenylenediamine, or both. Experiments are in progress by which we hope contingent upon the acetylating, and hence detoxifying, ability of the animal is to show that a riboflavin constituent of the diet, but conclusive results must await the development of improved technical procedures.

We had, then, established that paraphenylenediamine is a breakdown product of butter yellow which damages the Coenzyme I system *in vitro*. This is probably true also *in vivo*, because dimethylparaphenylenediamine kills the animal. We had not established, however, that this breakdown product is toxic to the respiration of living liver cells, and this evidence was next provided. Dimethylparaphenylenediamine 10^{-3} molar concentration sharply inhibited the respiration of normal rat liver slices. Hence our effect could be shown to hold not only for the isolated enzyme but also for the metabolic activity of liver tissue.

From the facts mentioned, one would suppose that the constant delivery of a strongly toxic compound to liver cells would result in a sharp reduction in the metabolic activity of those cells. This presumption was further supported by the facts already presented, which prove that in the course of butter yellow and basal diet feeding the contents of riboflavin and of nicotinic acid coenzyme,

or Coenzyme I, in the livers of the animals are very sharply reduced. Lastly, direct microscopic study of the livers of the treated animals provides direct evidence of distortion and apparent injury to the non-malignant cells. In view of all these facts, we were tremendously surprised to find that the livers of all the groups of animals, irrespective of the apparent damage or tumor formation, showed exactly the same oxidative power. The systems normally responsible for oxidation were seriously reduced, and yet anomalously the oxidative power remained normal. One explanation of this would be that a new or different oxidative system was at hand, and it did not depend upon either nicotinic acid or riboflavin for its action. This would be in accord with the studies of the Warburg school, which suggest that cancer cells do possess an abnormal metabolic enzyme.

The conclusion just stated leads to a very interesting and exciting thought. Casual inspection of the livers of the treated animals reveals good evidence that, whereas the normal liver tissue is damaged, the tumor tissue is growing actively and shows no evidence of toxemia. In all likelihood the toxic breakdown product of butter yellow is easily diffusible throughout the whole liver and is in contact with both normal and malignant cells. Since the normal cells are injured and the malignant cells are not, the cancer cell must be immune to the toxic breakdown product and probably so by virtue of its possession of the new or different resistant enzyme system just discussed.

This idea was subjected to experimental confirmation very easily. The effect of dimethylparaphenylenediamine on the rate of oxidation of a pulp of normal rat liver was tested. The compound was strongly toxic. When for the normal liver pulp tumor liver pulp was substituted, not only was no toxic effect observed, but the tumor tissue respired better than it did before the compound was added which poisons normal cells. This effect does not obtain for slice, however, and further experiments to elucidate this curious anomaly are in progress.

CONCLUSION

1. A protective, oxidative conversion of one carcinogen, dibenzanthracene, has been proved.

2. Protection against the carcinogenic effect of another chemical, butter yellow, by dietary constituents, of which one is riboflavin and another present in casein but as yet unidentified, has been established.

3. The induction of a conditioned deficiency of Coenzyme I in the affected liver cell by the feeding of a deficient diet plus butter yellow has been shown.

4. A metabolite of butter yellow which poisons the Coenzyme I system has been isolated and its poisonous effect demonstrated *in vitro* as well as *in vivo*.

5. The protective acetylation of this poisonous compound has been established.

6. It has been shown that under certain conditions the cancer tissue is immune to the metabolite which damages the normal cell and so presumably produces the cancer.

The next step in this study is obvious. Can a compound be found which will

reverse the phenomenon last mentioned, a compound which will damage cancer cells and leave normal cells unharmed? I only hope that this discussion may stimulate some one of you to engage in a search for that compound.

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A SHORT HISTORY OF THE TREATMENT OF ADDISON'S DISEASE

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The first comprehensive report of the clinical picture incidental to extensive destruction of the adrenal cortex was given by Addison in 1849 (1), although a fairly accurate clinical and pathological description of a case was presented by Bright (2) almost thirty years earlier. Bright, however, failed to appreciate the connection between the clinical and the pathological findings.

After Addison's description, almost twenty years elapsed before any substitutive therapy was attempted. During this twenty year period, patients with this disease were treated symptomatically, and particularly with "tonics" such as iron and arsenic. The first effort to treat this disease with adrenal extract was made by Stockman in 1867 (3). His results were entirely unsuccessful. From 1867 to 1903, Adams (4) collected a total of 97 cases from the literature in which organotherapy was employed in the form of desiccated whole adrenal and the desiccated extract and aqueous, alcoholic and glycerine extracts, used either by mouth or by injection. Of these 97 cases, 16 patients were "permanently improved." Among these was a patient who responded particularly well to a glycerol extract of fresh sheep adrenal glands given both by mouth and by hypodermic injection. When the use of the extract was discontinued, the patient was precipitated into acute adrenal insufficiency which terminated fatally. This case was reported by Osler (5) in 1896.

In 1895, Oliver and Schafer (6) succeeded in preparing watery, alcoholic and glycerine extracts of the adrenal glands which had considerable vasoconstrictor and pressor effect, obviously due to epinephrine. In the same year these investigators made extracts of the glands of patients with Addison's disease and found them lacking in the pressor substance which they had described as existing in normal glands. They, therefore, concluded that the deficiency of the pressor substance was the cause of Addison's disease. In 1903, Boinet (7) cautioned against the use of aqueous extracts which contain large amounts of epinephrine in the treatment of Addison's disease as opposed to the use of glycerin extracts which are relatively free of epinephrine.

With the isolation and synthesis of pure epinephrine hydrochloride, numerous reports appeared on the use of this drug in the treatment of Addison's disease. The earliest of these reports was by Raven (8) in 1904, who described "remarkable improvement" in one case treated with small amounts of this substance, while in our country, Symmers (9) reported the use of epinephrine hydrochloride by hypodermic injection and by mouth in a case treated for 143 days without noticeable improvement at any time. In 1920, Dr. Muirhead (10), who was himself afflicted with Addison's disease, described the beneficial effects of the

[1] This paper was originally planned to appear in the Anniversary Volume of this JOURNAL dedicated to Dr. B. S. Oppenheimer (Vol. 8, No. 5, 1942).

use of epinephrine hydrochloride which he took to the point of tolerance by mouth, rectum, and hypodermatically.

With the interest attached to the discovery of epinephrine, the possibility of the existence of other adrenal hormones was lost sight of until the middle 1920's, when attempts to isolate other potent cortical extracts were again resumed. It had already been learned by that time that epinephrine was of extremely meager value in the treatment of Addison's disease, and that it was incapable of maintaining the life of adrenalectomized animals.

In 1927, Rogoff and Stewart (11) succeeded in prolonging the survival period of adrenalectomized dogs with the use of saline extracts of whole adrenal glands. Whereas the average life span of control adrenalectomized dogs was 9.6 days, with the use of their extract, which they called Interrenalin, the survival period was prolonged to 14.2 days. In the same year, Hartman and his co-workers (12) described an adrenal extract which prolonged the life of adrenalectomized cats. This extract, in contrast to that of Rogoff and Stewart, contained no epinephrine. In 1929, Pfiffner and Swingle (13) described the successful use of an alcoholic adrenal extract in adrenalectomized dogs. In 1929, Rogoff and Stewart (14) described the use of glycerine extracts given both by injection and by mouth to 7 patients with Addison's disease. The results as reported were not particularly striking, although some improvement was evident.

The first striking result obtained by the use of cortical extract was described by Hartman and his co-workers (15) in 1930. Dramatic results were obtained in a patient in an acute Addisonian crisis with the use of their extract given subcutaneously and intravenously. In 1931, Rowntree, Greene, Swingle and Pfiffner (16) reported in detail the satisfactory results obtained in patients with Addison's disease treated with adrenal extracts prepared according to the method of Pfiffner and Swingle.

Following these initial reports, innumerable papers appeared confirming the life-saving qualities of potent cortical extracts in adrenal insufficiency both in experimental animals and in patients with Addison's disease, and a new chapter in hormone history had been written.

With the availability of a potent cortical extract, it now became possible to study the underlying electrolyte disturbances in clinical and experimental adrenal insufficiency, although some observations had already been reported on this point. Thus, Lucas (17) noted a low chloride level in the blood of adrenalectomized dogs. In the same year, Rogoff and Stewart (18) reported similar findings. In 1927, approximately one year later, Bauman and Kurland (19) observed a significant reduction in the levels of blood sodium, as well as of blood chloride, and an elevation in the plasma potassium, in adrenalectomized cats. In this interesting article they mention that several years previously they had observed beneficial effects following the use of salt solutions intravenously in experimental adrenal insufficiency. Loeb (20) was the first to describe the outpouring from the body of sodium and chlorides in the urine, their decrease in the blood, and the elevation of blood potassium in a case of Addison's disease. This was confirmed by Harrop, Soffer, and their co-workers (21, 22). These

latter investigators (21) suggested the use of a low salt diet as a provocative test in the diagnosis of Addison's disease. Even before a complete understanding had been achieved of the underlying disturbances in salt metabolism in adrenal insufficiency, the beneficial effect of salt therapy in this condition had been noted by several investigators. Soddu (23) as early as 1899, demonstrated that the symptoms of adrenal insufficiency in adrenalectomized dogs were somewhat alleviated by saline injections. In 1925, Stewart and Rogoff (24) reported an increase in the survival period of adrenalectomized dogs following the intravenous use of Ringer's solution given with glucose at frequent intervals. Similar results were obtained by several other authors, notably Corey (25), Banting and Gairns (26) and Marine and Bauman (27). The first successful treatment of a patient with Addison's disease with salt given intravenously, by rectum, and by mouth was reported by Loeb (28) and confirmed by Harrop, Weinstein, Soffer and Trescher (21). Harrop, Soffer, Nicholson, and Strauss (29, 30) succeeded in maintaining adrenalectomized dogs in normal condition over prolonged periods of time without the use of cortical extract but by the administration of salt alone. One dog was maintained in a normal state for a period of 5 months, at which time the experiment was voluntarily discontinued, the animal being precipitated promptly into insufficiency by the withdrawal of salt. In 1936, Wilder, Snell and their co-workers (31) further increased the efficacy of the treatment of Addison's disease by pointing out the importance and need for the restriction of the potassium intake in the diet.

By 1935, over three quarters of a century after the original description by Addison, the understanding of the underlying phenomena and treatment of the disease which bears his name had reached a fairly satisfactory level. The outlook of patients with this illness had improved considerably. The therapy was not curative, but substitute in type. A good deal, however, was still left to be desired. Moreover, hypoglycemic episodes occurred over which salt and the cortical extract unfortunately exercised very little effect. The pigmentation, so characteristic of the disease, remained immune to treatment. Cortical extract was difficult to obtain and was rather expensive, while the large daily doses of salt required were found burdensome by the patients. The first significant advances in the therapy of this illness, however, had been made.

Between 1936 and 1941, the important contributions to the treatment of Addison's disease consisted in the isolation of various crystalline fractions of the cortical hormone and their preparation synthetically.

In 1936 and 1937, Mason, Myers, and Kendall (32) and de Fremery and his co-workers (33) isolated corticosterone and dehydrocorticosterone in crystalline form from the extracts of the adrenal cortex and found that they could maintain adrenalectomized animals in good condition. A short while later, Steiger and Reichstein (34) announced the synthetic preparation of desoxycorticosterone acetate from stigmasterol and subsequently Reichstein and von Euw (35) succeeded in recovering this compound from an extract of the adrenal cortex. Levy-Simpson (36) used desoxycorticosterone acetate in the treatment of 2

patients with Addison's disease, and found that it exercised an effect qualitatively similar to that of adrenal cortical extract.

In 1938, Thorn, Engel, and Eisenberg (37) used desoxycorticosterone acetate in the treatment of bilaterally adrenalectomized dogs and found that it was effective in maintaining these animals in good condition despite a diet low in sodium and chloride. Withdrawal of the extract resulted promptly in acute adrenal insufficiency. Thorn, Howard, and Emerson (38) subsequently used this compound successfuly in 8 patients with Addison's disease without supplementary treatment with sodium salts or decrease in the potassium content of the diet. Ferrebee, Ragan, Atchley, and Loeb (39) treated 13 patients with intramuscular injections of desoxycorticosterone acetate or propionate, and found that improvement was greater than from any previous therapy. However, 3 of their patients developed hypertension, and 10 patients had edema of which 3 developed definite cardiac failure. Soffer, Engel, and Oppenheimer (40) reported the results of similar therapy in 5 patients with Addison's disease and confirmed the findings of the other authors. Emphasis was again placed on the attendant dangers of this therapy, the risks of hypertension, edema, and heart failure.

In 1937, Deansley and Parkes (41) reported that the subcutaneous implantation of pellets of estrogens and androgens produced a prolongation of the hormonal effect. Utilizing this technique, Thorn, Howard, Emerson, and Firor (42) implanted pellets of desoxycorticosterone acetate subcutaneously in 6 patients with Addison's disease and found that the results obtained with the pellets were similar to those of the intramuscular injections except that the former effected a greater economy in the use of the drug. Soffer, Engel, and Oppenheimer (40) implanted pellets in 4 patients and found that the risks associated with excessive absorption of the desoxycorticosterone acetate could be reduced by "underimplanting" that is implanting less pellets than is determined to be necessary by assay, and supplementing the therapy with daily small amounts of salt *per os*.

The use of desoxycorticosterone either by injection or by implantation represents a considerable advance in the treatment of Addison's disease. The material can be manufactured synthetically, it is much more potent than the old cortical extract, and in this respect much more economical. However, this new synthetic compound still has failed to solve the problem of pigmentation and of hypoglycemic episodes to which these patients are so prone. The steady advance in our knowledge of this disease and the isolation and identification of more and more active fractions of extracts of the adrenal cortex, however, offers hope that these problems, too, will be solved in the not too distant future.

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ELECTROENCEPHALOGRAPHIC STUDIES: A METHOD FOR DIFFERENTIAL DIAGNOSIS OF ABNORMAL ELECTROENCEPHALOGRAMS

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Electroencephalographic diagnosis is a purely empirical method. The fact that a particular type of electroencephalogram (EEG) has been found associated with pathology of verified type and localization, enables us to draw diagnostic conclusions when a similar record is found in another case. Electroencephalographic diagnosis, therefore, makes it necessary to compare records obtained from various subjects. A direct comparison of two or more records is difficult due to the great length of the records and the immense number of details which they include. The method to be described condenses the records into a small space, makes it possible to survey the essential content of a long EEG at a glance and so enables us to compare various EEGs with much less difficulty and much more accuracy.

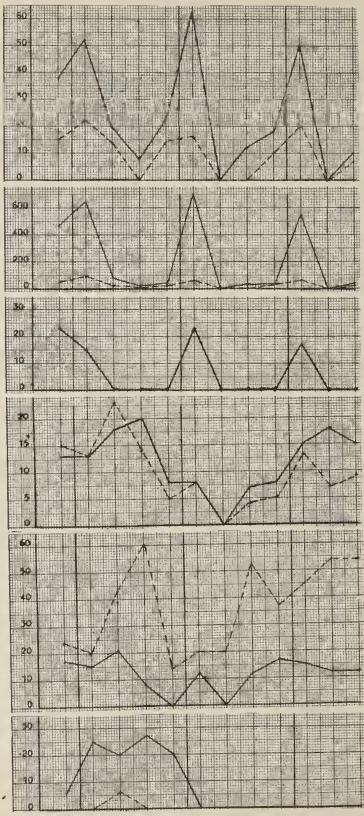
METHOD

Standard records were taken with a 3 channel Grass electroencephalograph using the following 11 electrodes: 1 vertex electrode (placed in the midline halfway between the nasion and the inion), 2 "indifferent" electrodes (placed on the right and left ear lobes), 4 pairs of symmetrical electrodes above the hemispheres, namely 2 frontal electrodes (placed $\frac{1}{2}$ the distance between the nasion and vertex and 3 cm. on either side of the midline), 2 central electrodes (placed 3 cm. lateral from the vertex electrode), 2 parietal electrodes (placed 4 cm. behind the vertex and 7 cm. on either side of the midline), 2 occipital electrodes (placed 3 cm. in front of the inion and 3 cm. on either side of the midline).

Records from symmetrical electrodes were taken simultaneously and the following leads were used: fronto-occipital; fronto-indifferent; centro-indifferent; parieto-indifferent; occipito-indifferent; fronto-vertex; centro-vertex; parieto-vertex; occipito-vertex; fronto-central; centro-parietal; parieto-occipital.

In analyzing records in which there appeared "irregular" delta activity with delta waves of various frequencies and amplitudes, the following procedure was followed. The per cent time delta (%tδ), which is the percentage of total length of record occupied by delta activity, was determined for each lead, measuring always at least 100 cm. of record. In this procedure potentials with a frequency of 6 or less per second and a voltage of at least 20 microvolts were considered as delta waves. The per cent time delta obtained for each lead was plotted on a graph (graph 1).

As the per cent time delta is not the only indicator of the degree of abnormality, an additional graph was made showing the "abnormality index" (AI) for each lead. The AI results from the application of the formula P/100 ×



Solid lines connect values from the left side, broken lines connect values from the right side. Numbers in vertical row indicate per cent time delta, except in graph 2 where they indicate the abnormality index. Letters in horizontal row indicate leads (F—frontal, C—central, P—parietal, O—occipital, I—indifferent, V—vertex).

Graphs: (1) left frontal leptomeningioma; (2) same case: abnormality index; (3) premotor meningioma in sagittal sulcus; (4) subarachnoid hemorrhage; (5) right parietal spongioblastoma multiforme; (6) left temporal arterial thrombosis.

10/F × V, or simplified P × V/10F. In this formula P means the per cent time delta, F the lowest delta frequency observed, V the highest voltage in microvolts with which this frequency appears.[1]

A comparison of graphs 1 and 2 shows the high degree of similarity between them. The graph, presenting the AI shows, however, that the relative degree of abnormality on the right is less high than it might appear from the graph presenting the per cent time delta.

TYPES OF RECORDS

The principle of electroencephalographic diagnosis with the aid of such graphs is that the graph obtained from an undiagnosed case is compared with the graphs of verified cases. From these graphs of verified cases the one most similar to that of the undiagnosed case should be selected. This selection is further simplified, and a direct comparison between two graphs becomes unnecessary when the various graphs obtained are divided into a number of well-defined groups. If this is done a newly obtained record is analyzed according to its classification with one or another of these groups.

Two characteristics of the graphs were used for this grouping: The amount of delta activity, and the degree of bilateral difference in delta activity. As to the amount of delta activity, records with a high and a low amount can be separated. (In the beginning of this work I distinguished between 4 degrees of abnormality. This subdivision was discarded because it was not a better diagnostic aid than the simpler subdivision employed at present). The difference between a high and low degree of abnormality is evident from a comparison of graphs 1 and 3. In order to arrive at an exact definition of the terms "high" and "low abnormality" the following criteria were used to obtain a safer determinant than that of a purely visual impression. High abnormality records show three of the following four characteristics: 1) An average per cent time delta of 20 or more; 2) an average AI of 60 or more; 3) a per cent time delta of at least 35 in one lead; 4) an AI of at least 150 in one lead. They also show a lowest frequency of 2 or less. Average per cent time delta and average AI mean the value obtained when the sum of the values for all leads on the more abnormal side is divided by the number of leads. A low abnormality record is a record in which the lowest frequency is not lower than 2 per second and in which two of the other values are lower than described above.

In separating records according to the degree of bilateral difference, the following types were differentiated: asymmetrical, parasymmetrical and symmetrical records. A symmetrical record is a record in which the delta activity is identical on both sides as to frequency, voltage and time of appearance (graph 3). A parasymmetrical record is demonstrated by graph 4, an asymmetrical record by graph 1. Objective values were developed to differentiate

[1] I am fully aware that a much more exact index of abnormality can be obtained by using such instruments as the analyzer described by Grass and Gibbs (3), but such instruments are only at the disposal of a few and simpler methods have to be devised for general use.

between asymmetrical and parasymmetrical records. In the following, delta quotient means the figure obtained by dividing the sum of the per cent time delta values of the higher abnormal side by the corresponding sum from the other side. The abnormality index quotient is obtained by applying the same formula with the values for the AI. Records with a high degree of abnormality are considered as asymmetrical when the delta quotient is higher than 1.5 or the AI higher than 2, while they are considered as parasymmetrical when the delta quotient is 1.5 or less and the AI quotient 2 or less. In records with a low degree of abnormality, asymmetry is characterized by a delta quotient or an abnormality index quotient higher than 2, a parasymmetrical record is present when both values are 2 or less.

So far, 6 types of records have been separated: A. High abnormality records: 1) asymmetrical, 2) parasymmetrical, 3) symmetrical, B. Low abnormality records: 4) asymmetrical, 5) parasymmetrical, 6) symmetrical. Each of these 6 groups was again subdivided into two subgroups according to the presence or absence of a well defined electroencephalographic focus in fronto-occipital direction. Graphs 1 and 3 demonstrate a focal increase of abnormal activity at the frontal electrode or electrodes. This increase is well lateralized in graph 1 and symmetrical in graph 3. Graph 4 shows a record without an electroencephlographic focus. In this graph there is no evidence of any one electrode from which a predominant degree of abnormality is recorded.

SOME CLINICAL CORRELATIONS

It seems too early and the material seems too small to give a copy of the table correlating the various types of records with all the clinical diagnoses falling into these groups. Only a more general correlation shall be given at present.

Records with an electroencephalographic focus: The great majority of cases in this group (90 per cent in my material) are space consuming lesions. The highly abnormal records are associated with the more active types of pathology (e.g., fast growing tumors of the gliogenous group, only a few meningiomas) and with different types of pathology involving the diencephalon. The latter show bursts of "regular" delta activity, composed of delta waves of one and the same frequency and voltage, superimposed upon the irregular delta activity. Records with a low degree of abnormality are associated with less active types of pathology (e.g., meningioma, chronic arachnoiditis, chronic subdural hematoma, rare cases of cerebral arterial thrombosis). Asymmetrical records occurred almost exclusively with lesions in the cerebral hemispheres. Parasymmetrical records were found associated with lesions close to the midline and records of this type with superimposed bursts of regular delta activity in early cases of post-concussion syndrome. Symmetrical records in the low abnormality group were found with slowly growing midline tumors (meningioma of the sagittal sulcus, ependymoma of the third ventricle, olfactory groove meningioma). Highly abnormal symmetrical records were found in cases of cerebrovascular syphilis with involvement of the diencephalon and in lymphocytic choriomeningitis.

Records without an electroencephalographic focus: Records of this type with a high degree of abnormality were frequently found associated with acute forms of a disease (e.g., subarachnoid hemorrhage, meningitis, encephalitis), the subacute and chronic forms of which show a low degree of abnormality. Asymmetrical records corresponded to focal lesions with additional diffuse damage (e.g., acoustic neuroma with internal hydrocephalus, subarachnoid hemorrhage with focal cerebral involvement). Parasymmetrical records were found in diffuse lesions with focal accentuation (e.g., encephalitis, early post-concussion syndrome) and again in focal lesions with diffuse distant effect. All our cases with tumors of the cerebellar hemispheres showed parasymmetrical records with a high degree of abnormality except those cases in which the EEG was entirely normal. Symmetrical records were associated with diffuse lesions (e.g., encephalitis) and with midline tumors with diffuse distant effects (pituitary tumors, pinealoma, tumors of the vermis).

LOCALIZATION

Some correlations between the type of EEG and localization of the lesion were discussed above. No mention was made of the localizing significance of increased delta activity at one or two particular electrodes. Just this fact is very easily visible in the graphs.

Asymmetrical graphs which show a focal increase at one of the electrodes placed above the hemispheres indicate a lesion very close to this electrode. Graph 1 shows a focus at the left frontal electrode and is taken from a case of leptomeningioma involving the second frontal convolution. Graph 5 shows how a focus at the right parietal electrode presents itself with this method. It is taken from a case of spongioblastoma multiforme (glioblastoma) of the right parietal lobe. An electroencephalographic focus at one of the indifferent electrodes shows a pattern as shown in graph 6 corresponding to a case of thrombotic lesion of the left temporal lobe.

Parasymmetrical and symmetrical records with increase of delta activity at two symmetrical electrodes point towards a lesion in or close to the midline, in or close to the frontal plane of these electrodes. Graph 3 is taken from a premotor meningioma in the sagittal sulcus. Similar graphs may be found in olfactory groove meningioma. Symmetrical accentuation of delta activity at both frontal electrodes was also found in lesions involving the diencephalon. In this case bursts of regular delta activity were superimposed upon the irregular delta activity.

In many cases with asymmetrical records the focal accentuation of delta activity occurs at two electrodes simultaneously. This may indicate a lesion between the two electrodes, e.g., a temporo-parietal tumor when delta activity is pronounced at the indifferent and parietal electrode. In other cases this accentuation at two electrodes indicates a deeply seated tumor in their vicinity, e.g., a tumor of the island of Reil when the indifferent and the frontal electrode show the highest amount of delta activity.

The method of localization with the aid of such graphs is not intended to dis-

place other methods of electroencephalographic localization as devised by Walter (4) and outlined very recently by Gibbs and Gibbs (2). It has been my experience, however, that the use of phase reversal phenomena fails frequently to give satisfactory results in cases with large tumors in which delta activity is widespread over one hemisphere.

OTHER TYPES OF ABNORMAL ELECTROENCEPHALOGRAMS

The abnormal electroencephalograms discussed in this paper are only those with irregular delta activity. There are many other types of abnormal electroencephalograms, e.g., electroencephalograms with the appearance of delta activity or spikes or combined patterns in bursts only, electroencephalograms with an abnormally low basic frequency and superimposed irregular delta activity without focal increase, electroencephalograms with an abnormal focal depression of delta activity and all the many variations described by Davis (1).

As far as diagnostic encephalography is concerned the aim is to obtain a description of all the various types of abnormal electroencephalograms and to state their clinical correlations. If this is done, a kind of diagnostic table will result which will make electroencephalographic diagnosis easier, more reliable and much better to teach than now. I hope that the method of analysis described in this paper will be of assistance in arriving at this aim.

SUMMARY

A method for the analysis and graphic presentation of electroencephalograms with irregular delta activity is described. A number of types of abnormal records is established and some clinical correlations of these types are given.

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CHRONIC TUBERCULOUS EMPYEMA; CONSERVATIVE THERAPY

Case Report

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The radical cure of the draining, chronic tuberculous empyema cavity is a surgical procedure of great magnitude and the percentage of successes is none too large. Fortunately, in a considerable number of these cases, the underlying pulmonary disease has been arrested. On the other hand, the long duration of the pleural infection has resulted in such thickening of the visceral pleura that pulmonary reexpansion cannot be attained. Usually the presence of a bronchopleural fistula is a complicating factor.

After adequate drainage (necessitated by secondary infection) of the pleural space has been instituted, the empyema in itself will not lead to a fatal termination. A progression of the pulmonary process or the onset of amyloid disease, due to chronic suppuration, are the principal causes of death. If the patient first comes under observation many years after the pleural infection has begun, one may assume that he has permanently escaped both of these complications. Under such circumstances, in carefully selected cases, conservative surgical treatment of the empyema cavity may be considered.

The case report presented here is of a patient who was first seen eleven years after his initial pleural infection. During this period, he undoubtedly had a large empyema cavity with relatively few symptoms. He had undergone an appendectomy and a gastroenterostomy during that period. On admission he was 50 years old and was decidedly underweight. Adequate drainage of the empyema cavity was instituted and the parietal pleura was found to be markedly thickened and calcified. The ribs showed miliary tubercles on pathological examination although no tuberculosis was found in a piece of excised parietal pleura. The finding of tubercles in the ribs substantiated the assumption that the initial infection was probably tuberculous in origin.

In view of the age and poor general condition of the patient, as well as the chronicity of the lesion, it was felt that he might do as well with conservative therapy as with radical surgery. The extent of the empyema (from diaphragm to apex) would have necessitated a many-stage thoracoplasty. The calcification of the parietal pleura would have required the addition of a "Schede type" procedure. The presence of a bronchial fistula lessened the chances of complete cure. The inability to find tubercle bacilli in the sputum or tubercles in the pleura indicated that this element of the infection was arrested or "burnt out."

The patient was discharged and has been followed for the past eight years. During this time he has remained well and has worked continuously at a rather arduous occupation. The empyema cavity has diminished considerably in size and drains about one ounce of mucopurulent material through a skin-lined sinus. The broncho-pleural fistula is still present but causes no symptoms.

He has regained the weight lost during the early years of his illness and there is no evidence of amyloid disease.

CASE REPORT

History (Adm. 351151). A white man, aged 50 years was admitted to the hospital April 19, 1933. Eleven years prior to admission the patient had "influenza," pleurisy with high temperature, and cough productive of much sputum. This episode ended with severe dyspnea for which two ribs were resected, with evacuation of considerable pus from the pleura. Tube drainage was maintained for three months following which the wound closed. Five months after closure, the wound had to be reopened and a tube was kept in place for five years. The drainage tube was then removed and the wound again healed. He was perfectly well in respect to his chest condition for the next six years. In 1930 he underwent a gastroenterostomy for a duodenal ulcer and an appendectomy was also performed.

Eight months prior to admission, he noticed the drainage of a small amount of thick, odorless pus from the old chest wound. Two months later he had "grippe" with cough and sputum which was of the same character as the drainage from the wound. There were no constitutional symptoms. Methylene blue injected into the sinus appeared promptly in the sputum.

Examination. "The patient is a thin, chronically ill man. There are practically no respiratory movements of the left chest. The entire left chest presents diminished fremitus most marked in the lower axilla below the seventh rib and below the fifth rib posteriorly. There is marked dullness over this same area. Below this, breath voice and whisper are all amphoric in quality, this being most marked over the area of the discharging fistula and diminishing with distance from this point. There is marked clubbing and cyanosis of the fingers and toes." Sputum examinations for tubercle bacilli were negative. Preoperatively the diagnosis of chronic recurrent empyema with broncho-pleural fistula was made and operation was performed April 21, 1933.

Operation. "Thoracotomy and rib resection with drainage, for chronic empyema, left, with broncho-pleural fistula. Skin incision made in postero-lateral aspect of the chest in region of existing sinus tract. Extensive bridging of bone was removed, together with three-inch segments of the seventh and eighth ribs. The parietal pleura was exposed and excised. This was one-half inch in thickness, markedly fibrotic and calcified. The surface of the lung was remarkably mobile and came up almost to the chest wall on coughing or straining. Situated in the region of the anterior axillary line, there was a funnel shaped depression which marked the site of a freely blowing bronchial fistula. The empyema cavity extended from the region of the diaphragm below, well up to the apex, and occupied the axillary and posterior aspects of the chest. The cavity was loosely packed with gauze."

Pathological report: "Piece of pleura showed acute and chronic inflammation; bone marrow of ribs showed miliary tubercles."

Course. The patient made an uneventful postoperative recovery and was discharged on May 17, 1935 with a clean, granulating empyema cavity, broncho-pleural fistula and draining sinus.

He has been seen at regular intervals since discharge. The last examination was performed on January 7, 1941. During this time the patient has remained in good health. He has no cough or sputum. He has regained his weight and has worked regularly at his original occupation. The sinus has become skin-lined and required no tube or packing to maintain the orifice. There is drainage of about one ounce of mucopurulent material daily, requiring one change of dressing in the morning. The broncho-pleural fistula is still present but causes no symptoms.

X-ray examination of the chest on January 7, 1941, with the injection of iodized oil through the sinus, was reported as follows: "Examination of the chest shows a marked thickening of the pleura over the left lung as was described on the examination of April 20, 1938. Since that time there has been a further flattening of the left chest and there has

appeared a considerable amount of calcium deposit in the residual cavity in the pleura extending from the level of the resected eighth rib to the eleventh rib in the region of the posterior costophrenic sinus. There is a small fluid level at the site of the resected ninth rib. Iodized oil injected through the sinus tract, outlines a cavity in the pleura in the region of the operative site extending upward from the external sinus for a distance of $3\frac{1}{2}$ inches. The tract is only about $\frac{3}{4}$ inch in width. This communicates with the bronchial tree. The latter, however, is not well outlined. Only the paravertebral division of the left upper lobe is well filled with the oil and this shows a terminal sacculation at about the level of the fourth intercostal space."

DISCUSSION

A case is reported which illustrates the application of conservative therapy in chronic tuberculous empyema. When seen within a reasonable time after the onset of pleural infection, secondarily infected tuberculous empyemata should be treated in the usual manner, with eradication of the empyema cavity as the ultimate aim. If first seen after a protracted period when the infection has become quiescent, conservative therapy may be indicated in carefully selected cases.

SUPPURATIVE THYROIDITIS WITH STREPTOCOCCUS VIRIDANS BACTEREMIA; RECOVERY FOLLOWING SURGICAL DRAINAGE

MYRON A. SALLICK, M.D.

[*From the Surgical Service of Dr. John H. Garlock*]

Acute inflammatory lesions of the thyroid are rarely encountered. At this hospital, during the past ten years, less than a dozen such cases have been observed. Except for the one reported here, all of these subsided spontaneously without suppuration. The occurrence of a case of suppurative thyroiditis merits recording, particularly since this is the only instance known to the writer in which a complicating streptococcus viridans bacteremia was observed.

CASE REPORT

History (Adm. 467494). E. S., aged 30 years, a German refugee housewife, was admitted to the hospital on January 6, 1941. Her past medical history was apparently negative aside from an appendectomy in childhood. She stated that she had been entirely well until six days before admission when she suddenly experienced pain in the midline of her neck anteriorly. On the following day her temperature rose to 103°F. and her neck became swollen. Fever persisted, the swelling increased, and swallowing became difficult and painful. These symptoms grew progressively worse.

Examination. The patient appeared acutely ill. Her temperature was 103°F., her pulse rate was 160 per minute and her respirations were 24 per minute. A large, firm, tender, non-fluctuant mass occupied the isthmus and right lobe of the thyroid, displacing the trachea to the left. The pharynx was slightly congested. Laryngoscopy was negative. The heart showed no abnormality, and systematic examination was essentially negative.

Laboratory Data. The white blood count was 18,000 with 84 per cent polymorphonuclear leucocytes. The blood Wassermann reaction was negative. Culture of the blood made on the day of admission yielded no growth. The urine contained a trace of albumin. An electrocardiogram was normal.

Course. Symptomatic and supportive treatment was instituted. In addition wet dressings were applied to the neck and sulfanilamide, 1.0 gram every 4 hours, was given by mouth. The patient, however, did not improve. Her temperature rose to 104.4°F. and her pulse rate ranged as high as 156 per minute. The swelling in her neck became larger and brawnier but no fluctuation could be detected. She began to develop dyspnea and her dysphagia increased. Sulfanilamide was replaced by sulfathiazole, 1.0 gram being given orally every three hours.

On the evening of the third day following admission, the patient had a severe shaking chill with elevation of temperature to 106.4°F. She appeared more toxic, and was dyspneic and cyanotic. She had an extremely rapid pulse. The leucocytosis rose to 37,500 with 86 per cent polymorphonuclear leucocytes. A second blood culture was taken. Slight softening was now detected over the right lobe of the thyroid. This site was aspirated by needle and foul smelling pus was withdrawn. Operation was, therefore, performed promptly.

Operation. Under local anesthesia by means of procaine hydrochloride (1.0 per cent), a transverse incision was made over the right lobe of the thyroid. Marked edema and induration of the subcutaneous tissues and of the prethyroid muscles were noted. The right lobe was exposed, an aspirating needle was again inserted, and a large amount of thick pus having a foul odor was removed. The gland was then incised and a large abscess cavity was opened. The entire right lobe and isthmus appeared to be the seat of a large abscess containing about two ounces of pus under tension. The abscess was also found to have a

short extension downward where it had ruptured beneath the overlying muscles. The left lobe of the thyroid was not involved. The pus was evacuated and two grams of sulfanilamide crystals were inserted into the abscess cavity together with a loose packing of plain gauze. The wound was not sutured. The specimen removed at operation consisted of necrotic tissue with purulent exudate.

Bacteriology. The blood culture taken immediately before operation yielded streptococcus viridans in all flasks. Culture of the pus removed at operation revealed streptococcus viridans and streptococcus hemolyticus. The postoperative blood cultures were negative.

Postoperative Course. Improvement following operation was prompt and striking. The temperature fell sharply to 100.4°F. and then decreased gradually to normal in six days. There was practically no drainage from the wound after the first few days. After removal of the packing on the fourth day, the wound margins promptly fell together. The patient left the hospital on the tenth day after operation and has remained well. The wound healed with a fine scar. It was subsequently learned that the patient had previously exhibited some evidences of hyperthyroidism. When last seen, however, she had no symptoms or signs of thyroid dysfunction.

COMMENT

Being ductless and surrounded by a dense enveloping capsule, the thyroid is rarely involved by contiguous suppuration. Metastatic abscess of the thyroid is exceptional, even in general pyemia, although instances occurring in the course of puerperal sepsis, typhoid fever and erysipelas are known. On the other hand, the thyroid is rather vulnerable to infection spreading through lymphatic channels, usually by extension from the upper respiratory passages. A notably high incidence of this type of thyroiditis is seen in Graves' disease. In most instances such inflammation is interstitial and subsides spontaneously in a few days.

The clinical picture of acute suppurative thyroiditis is well exemplified in the case cited. The onset was sudden with neck pain, local swelling, fever and tachycardia. Brawny induration over the thyroid was prominent. Leucocytosis became marked early in the illness. Increasing systemic intoxication with chill and high fever, cyanosis, dyspnea, and dysphagia suggested the presence of extensive thyroid suppuration. Fluctuation was difficult to detect even with extensive necrosis, because of the thickness of the edematous overlying muscles and the tough capsule of the gland made tense by the abscess. For this reason, it should be stated generally that when suppuration is suspected, surgical drainage is indicated without waiting for typical fluctuation to appear. If operation is delayed, the pus may rupture into neighboring structures such as the trachea, the esophagus, the great vessels or the mediastinum. Moreover, all or most of the gland may be destroyed by infection and myxedema may result.

In the present case, loss of half of the gland, amounting practically to a hemithyroidectomy, may have been actually beneficial since it was later learned that this patient had previously manifested symptoms of hyperthyroidism (cf. marked tachycardia) which, postoperatively, were no longer evident. Hyperthyroidism may conceivably have had a localizing effect in bringing about suppurative thyroiditis in this case, since as already mentioned, non-suppurative interstitial thyroiditis is not infrequent in Graves' disease complicated by

pharyngeal infections. Mixed infection by streptococcus viridans and streptococcus hemolyticus probably accounted for the severity of the lesion in this case. The presence of streptococcus viridans in the second of two blood cultures is interpreted as the result of a transient bacteremia.

SUMMARY

A case of suppurative thyroiditis is described in a young woman with probable Graves' disease. At operation an abscess was encountered destroying half the gland. Culture of the abscess revealed mixed infection with streptococcus viridans and streptococcus hemolyticus. Transient bacteremia with streptococcus viridans was also noted pre-operatively. The patient recovered promptly and on later examination was found to be free of all evidences of hyperthyroidism.

FISH-BONE PERFORATION OF MECKEL'S DIVERTICULUM

VERNON A. WEINSTEIN, M.D.

[*From the Surgical Service of Dr. Ralph Colp*]

The persistent proximal segment of the fetal omphalomesenteric duct, known since 1809 as Meckel's diverticulum, is found in about two per cent of routine autopsies, and in the majority of cases causes no symptoms. One may gain some idea of the infrequency with which pathological changes occur in a Meckel's diverticulum from Abrams' (2) report of eighty-eight cases, seventy-nine of which represented asymptomatic anomalies found in 1.3 per cent of their routine autopsies.

Meckel's diverticulum is subject to a number of pathological changes. Inflammation may occur similar to that seen in the vermiform appendix, ranging from simple catarrh to an extensive gangrene (3). Lesions are also produced by the occasional occurrence in the diverticulum of heterotopic tissue histologically typical of gastric or duodenal mucosa or of pancreatic parenchyma. This misplaced tissue is liable to ulceration closely resembling that of gastric or duodenal peptic ulcer. These ulcers may bleed copiously into the bowel lumen or perforate into the free peritoneal cavity (4). Adenomata have been known to arise from heterotropic pancreatic tissue within a diverticulum (5).

Intestinal obstruction is not uncommonly caused by a Meckel's diverticulum. This may be the result of inversion of the diverticulum into the lumen of the small bowel with subsequent intussusception in which the diverticulum forms the head of the invaginated portion (6, 7). Mechanical ileus may also result from twists or kinks of adjacent loops of intestine about a diverticulum in which the distal end is either free or fixed to the umbilical region by an obliterated fibrous congenital band. Halstead (8) in 1902 stated that Meckel's diverticulum was responsible for six per cent of all cases of intestinal obstruction. It is probable that the ratio is less at the present time because of the intervening forty years of greatly increased surgical activity with its attending incidence of obstruction by postoperative adhesions.

An uncommon complication is perforation of the diverticulum by a foreign body. Donovan (9) reported a case perforated by a wooden splinter. A second case is mentioned by Peterson (9) in his discussion of Donovan's paper. Williams (10) placed on record a case of fish-bone perforation of Meckel's diverticulum with operative recovery. Persson (11) succeeded in finding twelve such cases in the literature and reported three more of his own. He found the onset of symptoms to be milder than in perforation of an ulcer of Meckel's diverticulum or acute inflammation. Initial symptoms are few, the temperature is usually sub-febrile, and signs of peritonitis are moderate. His findings correspond closely with those of the writer's case.

The diagnosis of Meckel's diverticulum is most often made at operation or postmortem but may be made clinically. Certain symptoms may lead the canny diagnostician to a correct conclusion. Profuse bright red hemorrhage from the

bowel in children or young adults may indicate ulceration or erosion of heterotopic gastric mucosa in a Meckel's diverticulum. Acute peritonitis in a young adult with a previous history of bowel hemorrhages may signalize a perforating ulcer of Meckel's diverticulum. A history of a slowly healing unbilicus after birth, or of persistent umbilical fistulae or adenomata in infancy, taken together with either of the above symptom complexes, would bear strong evidence in favor of the diagnosis of Meckel's diverticulum.

Peri-umbilical colic and tenderness are said to occur with Meckel's diverticulitis. Stewart (12) states that a pathognomonic sign is localized tenderness on the right side, above McBurney's point and at about the level of the umbilicus.

Diagnosis of Meckel's diverticulum may be made on x-ray examination by the use of small amounts of barium and frequent fluoroscopic examinations demonstrating a persistence of barium in the terminal ileum. The diagnosis is otherwise admittedly difficult but there is one occasion when it is inexcusable to miss it and that is at the time of surgical exploration. The practice of removing an innocuous or questionably inflammed appendix, when operating for acute abdomen, without inspection of the terminal 24 inches of ileum for a Meckel's diverticulum cannot be condoned.

CASE REPORT

History (Adm. 466568). The patient, a 54 year old man had an appendectomy eight years prior to admission. He entered the hospital December 14, 1940 stating that eight hours previously he began to have cramp-like peri-umbilical and right lower quadrant pain. The pain did not radiate. At first, there was no nausea, but as the pain increased in severity both nausea and vomiting occurred.

Examination. The patient was a well nourished individual. His upper respiratory tract, heart, and lungs were normal. An old right lower rectus abdominal scar was present but there was no hernia. Tenderness was marked about the upper end of the scar and there was moderate spasm of the right rectus muscle. The temperature was 99.2°F., his pulse was 80 per minute and respirations 20 per minute. The hemoglobin was 82 per cent. White blood cells 11,000, with normal differential count.

The history of a previous laparotomy and of vomiting suggested the possibility of low intestinal obstruction but the signs of peritoneal irritation made delay seem unwise. Laparotomy under spinal anesthesia was therefore performed by Dr. Ralph Colp.

Operation. A considerable number of omental adhesions were encountered. The peritoneal cavity contained a moderate amount of clear amber fluid. A Meckel's diverticulum was discovered on the anti-mesenteric surface of the terminal ileum and through its apex was seen protruding a fine fish bone. The adhesions were freed, and a loop of ileum containing the diverticulum was brought out through the wound and an intestinal clamp was applied across it. An elliptical incision was made through the wall of the ileum at the base of the diverticulum and the latter was excised. The opening in the ileum was repaired in two layers, the line of closure being transverse to the long axis of the bowel. The abdomen was closed in layers.

Pathological examination was made by Dr. S. Otani who described the specimen as a resected Meckel's diverticulum which measured 2.5 cm. in length and 2 cm. in width. Its serosa was somewhat dull and covered by a thin film of pinkish gray fibrinous exudate. Projecting through the distal end of the diverticulum was a fish bone. On section the mucosa in the vicinity of the perforation presented an area of yellowish gray discoloration and ulceration. The entire fish bone measured 2 cm. in length, 0.5 cm. of which had penetrated the serosa.

FIG. 1. Specimen of Meckel's diverticulum opened to show fishbone in place

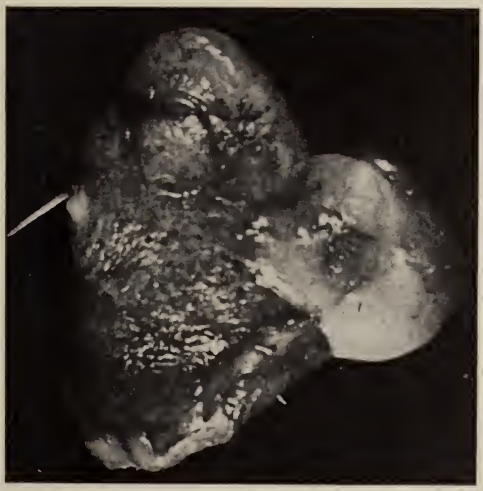

FIG. 2. Meckel's diverticulum unopened. The fishbone is to be seen projecting from the serosal surface. The serosa at this point is covered by gray exudate.

Postoperative Course. The postoperative course was uncomplicated. Sulfanilamide solution (0.8 per cent) was given intravenously for the first thirty-six hours. The patient left the hospital asymptomatic on the thirteenth postoperative day.

When questioned subsequently the patient recalled vividly having swallowed and choked on a fish bone about six weeks prior to his operation.

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CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

Wednesday, January 3, 1940

Essential Hypertension; Splanchnic Nerve Resection. Death Due To Congestive Heart Failure.

[*From the Medical Service of Dr. B. S. Oppenheimer*]

History (Adm. 446757; P.M. 11340). This was the first admission of a forty-three year old man, who complained of dyspnea, anorexia, weakness, and muscle twitching. Four years before admission he was told that he had hypertension. He was asymptomatic until two and a half years later when he developed dyspnea, cough, orthopnea and severe headaches. One year before admission, he had a very severe attack of dyspnea. He was then digitalized with great relief. However, the dyspnea and especially the severe pain in the head and neck recurred. Pain across the chest appeared. Three and a half months before admission his blood pressure was said to be 230 systolic and 140 diastolic; the heart was enlarged; a systolic murmur was present. There was no edema and the abdominal viscera were not palpable. The fundi showed a hypertensive neuroretinitis. The urine concentrated to 1.018, and showed a trace of albumin, one to two red blood cells per high power field, and an occasional granular cast. The blood urea nitrogen was 34.4 mg. per cent. Electrocardiogram showed left axis deviation, depression of the ST, inverted T-waves and prolongation of the P-R interval. A splanchnic section, and dorsal sympathectomy and ganglionectomy were performed. Immediately postoperatively the blood pressure fell to 180 systolic and 110 diastolic, but gradually rose to 220 systolic and 145 diastolic. About three weeks after operation he became progressively more dyspneic and orthopneic; for the first time he noted ankle edema. Many moist râles, as well as gallop rhythm were now present; the liver was palpable. He was treated with digitalis and diuretics. He experienced subjective relief in that the head and neck pain subsided and did not recur. He continued to be very dyspneic, orthopneic, edematous and had developed extreme weakness and anorexia. Pruritus and muscular twitchings appeared. The family history revealed that his mother had died of a coronary thrombosis, and that a sister had hypertension.

Examination. The patient appeared chronically ill, dyspneic, and restless. The sclerae were icteric. The discs were pale with sharply defined edges. The arteries were narrowed and copperwire in appearance. Numerous hemorrhages were seen in both fundi, more marked on the right. There were râles and slight dulness at both lung bases. The heart was enlarged to the left. Rhythm was regular; the second aortic sound was accentuated. The blood pressure was 220 systolic and 140 diastolic. Moderate peripheral sclerosis was present. The abdomen was distended; there was dulness in the flanks and a fluid wave was elicited. A tender liver was palpable below the umbilicus. There was pitting edema of the sacrum and ankles.

Laboratory Data. Blood: Hemoglobin, 77 per cent; red blood cells, 4,670,000; white blood cells, 15,000 with 74 per cent polymorphonuclear neutrophiles, 20 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophiles. The urine, which showed a maximum specific gravity of 1.020, contained a trace of albumin, urobilin in a 1 to 160 dilution, 4 to 6 white blood cells, and rare red blood cells. The venous pressure was 16.5 cm. with a rise to 22.5 cm. on right upper quadrant pressure. Saccharin circulation time was 50 seconds. Sedimentation time was normal. Blood chemistry showed a urea nitrogen of 30; sugar, 110; sodium chloride, 575; cholesterol, 255; ester, 100; calcium, 9.4; phosphorus, 4.5 mg. per cent. The total protein was 6.2 per cent. Icterus index, 9; bilirubin, 0.2 gm.; Van den Bergh, negative. Blood Wassermann reaction, negative. Takata-Ara, 4 plus.

Course. The patient was given oxygen, digitalis, and esidrone. He responded fairly well, so that the edema disappeared and the liver edge receded. About two weeks after admission, it was noted that his blood pressure had dropped to 120 systolic and 90 diastolic; he was extremely dull and unresponsive. Clinically it was thought that a myocardial infarction could be responsible. This was substantiated by electrocardiographic changes in the form of a large Q_4 and further inversion of T_3 and T_4, suggestive of a recent anterior wall infarction. He rallied from this state and in a week his blood pressure had returned to hypertensive levels. Although by now most of the evidences of congestive heart failure had disappeared, the liver and a firm spleen were palpable. The icterus persisted, and in fact, the index rose at one time to 20. The possibility of a hemolytic icterus, cirrhosis of the liver, or even an acute transient hepatitis were considered, in view of the apparent nonrelation to the cardiac status. The fragility test was normal.

Attacks of paroxysmal dyspnea continued as well as complaints of nausea, headache and chest pain. On one occasion a gallop rhythm was heard. His general condition remained essentially unchanged for the rest of his hospitalization. He died suddenly during sleep.

Necropsy Findings. The *heart* was enlarged. This included the right ventricle as well as the left. The anterior portion of the septum, on section, showed distinct mottling with many bluish-red subendocardial areas. The involved portion was slightly vascular and undergoing early organization. Corresponding with this subacute myocardial infarction, there was a complete obliteration of the ramus descendens anterior by a recent thrombus superimposed on a thick sclerotic plaque. The age of the thrombus and infarct coincided. A small infarct was present in the *lung.* The *kidneys* presented a uniformly granular surface.

The small *blood vessels,* in other organs displayed a marked intimal thickening, with markedly narrowed lumens. The thickening was a result of cellular intimal proliferation.

Comment. Dr. Klemperer. The very cellular intimal proliferation present in the arterioles stamps this case as an accelerated, rapidly progressive type of arteriosclerosis. These cases need not all die of renal insufficiency, and death may be cerebral or cardiac.

Dr. Baehr. Patients with so-called malignant hypertension upon whom splanchnic nerve resection is performed, invariably are relieved of their headache, which of course is a classic part of the hypertensive symptomatology. In addition, the fundal lesions of neuroretinitis may be reversed and normal vision due to absorption of hemorrhages, exudates and papilledema may be reestablished. In a small percentage, the hypertension itself has been reduced for a time. However, this operation is certainly not the last word in the therapy of arterial hypertension.

Reported by *Max Ellenberg, M.D.*

Wednesday, January 8, 1941

Exfoliative Dermatitis (Venenata) Due to "Elkay," A Proprietary Insecticide. Mural Staphylococcus Endocarditis

[*Private patient of Dr. W. Leifer*]

History (Adm. 465180; P.M. 11673). A 54 year old dentist was first admitted to the hospital September 23, 1940 because of a universal itching eruption of four months' duration. The past history indicated that thirty years before he had had eczema of the hands which responded promptly to x-ray therapy. The present skin condition began with involvement of the hands and it gradually spread to involve the entire body. During that time he had lost 40 pounds in weight, and was in a markedly weakened condition. A considerable amount of local therapy had been of no avail.

Examination. He was a well developed man busily engaged in scratching his skin. The skin presented a universal eruption which was red, scaling, and in places lichenified. No vesicular lesions were present, and the mucous membranes were uninvolved. The pupils were normal. The tongue was red and somewhat atrophied. The heart was not enlarged. The blood pressure was 140 systolic and 74 diastolic. The lungs were clear. A firm liver edge was palpable three fingers below the costal margin. Large, firm nodes were felt in the inguinal region.

Laboratory Data. Blood: Hemoglobin, 86 per cent; red blood cells, 4,900,000; white blood cells, 12,600 with 69 per cent polymorphonuclear leucocytes, 21 per cent lymphocytes, 2 per cent monocytes, and 8 per cent eosinophiles. The blood chemistry findings were as follows: sugar 85 mg. per cent; urea nitrogen 7 mg. per cent. The urine was negative for arsenic. Biopsy of the skin was reported to show changes somewhat suggestive of severe psoriasis, but not typical. The findings were compatible with an ordinary dermatitis of the chronic type.

Course. It was felt that the patient was suffering from an exfoliative dermatitis superimposed on a dermatitis venenata. The nature of the offending substance was unknown. Because of the fact that the patient had not been pursuing his profession for some time it was felt that the offending substance would not be found in the materials he handled professionally. The search narrowed down to three possible offending substances, namely, a bed spray, a proprietary deodorant called "Elkay," and a perfumed toilet water. These three substances were left in his room and by the next day the skin condition had become markedly aggravated. Investigation revealed the fact that the bottle of Elkay was improperly stoppered so that a considerable amount of this substance had volatilized and permeated the air of the room. This, therefore, seemed to be the offending substance. It was, therefore, completely eliminated and with the aid of general skin therapeutic measures he showed considerable improvement in the local as well as his general condition. He was discharged from the hospital October 5, 1940.

Second Admission. After discharge he was given fractional doses of x-ray at weekly intervals. The skin condition continued to improve. The day before the second admission (November 12, 1940) he suddenly became acutely ill. He became confused; his respirations increased markedly; his temperature rose to 104°F.; the pulse rate was 124 per minute; and he complained of some chest pain. At no time did the patient receive hypodermic, intramuscular or intravenous injections.

Examination. The skin condition was found to be much improved. The patient, however, was disoriented and uncooperative. The heart now appeared to be enlarged, the sounds were of poor quality, and a gallop rhythm was heard. The lungs showed dulness

at both bases with bronchovesicular breath sounds over the lower left lobe and a few crackles at the right base.

Laboratory Data. Blood: Hemoglobin, 70 per cent; red blood cells, 3,630,000; white blood cells, 13,200 with 93 per cent polymorphonuclear leucocytes, 4 per cent lymphocytes, and 3 per cent monocytes. The urine showed a faint trace of albumin and a rare hyalin cast. No pneumococci were recovered from the sputum.

Course. The temperature remained at about 104°F. for the rest of his stay. He was treated with chemotherapy but there was no response. He became rapidly stuporous, incontinent, respirations became more labored, and he died on the day after admission.

Necropsy Findings. Dr. Klemperer. The *heart* showed a most unusual lesion. On the mural endocardium of the left ventricle at the apex and extending upwards for about one inch was an irregular, plaque-like lesion. It lay like a thick membrane and appeared to be verrucous. A similar lesion was present on the right side of the intraventricular septum as well as in the posterior wall of the right ventricle. On cross-section, the granulous, verrucous appearance was evident; the plaque was several millimeters thick, grayish, and gelatinous. The underlying musculature was sharply defined. Microscopically, the lesion showed bacterial vegetations beneath which there was a layer of necrotic tissue, which, in turn, overlay a layer of granulation tissue. The coronary artery supplying this area was perfectly normal; the heart valves were completely uninvolved.

The *kidneys* were riddled with multiple embolic Staph. aureus abscesses. The *larynx* showed multiple petechiae in the mucous membrane.

The endocardial involvement in this case completely simulates the pathological findings as they occur in a valvular bacterial endocarditis. A most unusual feature is the chronicity of the endocardial infection with Staphylococcus aureus. There is clear histologic evidence of its long-standing duration with attempts at healing. It is, however, difficult to establish the pathogenesis of this lesion. The uninvolved valves eliminate the assumption of a preexisting rheumatic mural endocarditis and the normal coronary supply removes the possibility of a preceding myocardial infarction with an endocardial plaque which became infected. Hence, one must reason that the lesion arose either directly as a primary endocarditis, or else that a few mural abscesses in the myocardium broke through to the surface.

Comment. Dr. Baehr. In regard to the origin of the endocardial lesion, I am inclined to the belief that it arose from mural abscesses in the myocardium that broke through to the surface. This view is based upon: 1) the multiplicity of the lesions; 2) the presence of foci of interstitial inflammation in the myocardium, some of which are quite old; and 3) the fact that this mechanism would be quite analogous to the situation in Staphylococcus aureus infection of the kidney, namely an infection entering through the skin which is then disseminated to the involved organ. There then follows a latent period and then a sudden, severe bacteremia. There must, of course, have been a primary bacteremia.

Reported by *Max Ellenberg, M.D.*

CLINICAL NEUROPATHOLOGICAL CONFERENCE

Joseph H. Globus, M.D., *presiding*

Monday, February 10, 1941

Case 5.[1] Massive Cerebral Hemorrhage

[*From the Neurological Service of Dr. I. S. Wechsler*]

History (Adm. 450691; P.M. 11384). A colored woman, aged 42 years, entered the hospital on January 3, 1940. About 1½ hours prior to admission she arose to prepare for an automobile trip. She noted numbness of her left hand and there was a sense of stuffiness in her left ear. Shortly thereafter she had an attack of vomiting and complained of severe left temporal headache. Her speech became slurred and the entire left side of her body became paralyzed. She had been apparently well until two years before when she became subject to occasional bitemporal headaches and had an occasional epistaxis. She had no knowledge of hypertension, kidney disease or syphilis. She had borne nine children. Recently her menstrual periods had become irregular.

Examination. The patient appeared to be well developed and well nourished. She was semi-comatose responding to painful stimuli at first, but not later as the coma deepened. Her heart was enlarged to the left beyond the mid-axillary line, but no murmurs were heard. Her blood pressure was 168 systolic and 100 diastolic. The lungs and the abdomen were not abnormal. Her pupils were miotic, equal, and reacted very sluggishly to light. The fundi were poorly visualized, but after dilatation the retinal vessels appeared narrowed and "silver-wire" in appearance. Her eyes tended to deviate to the right. There was a suggestive left facial paresis. The right arm was somewhat spastic and there was complete flaccid paralysis of the left arm and left leg. The deep reflexes were absent in the left lower extremity, but were present in the other extremities. The abdominal reflexes were not elicited. There was a Hoffman sign on the left side, but no Babinski sign. There was complete left hypalgesia and hypaesthesia.

Laboratory Data. Urine analysis revealed a large amount of sugar. Blood: sugar, 215 mg. per cent; ureá nitrogen, 35 mg. per cent; chloesterol, 240 mg. per cent; white cell count, 24,900 with 86 per cent polymorphonuclear leucocytes; red cell count, 6,170,000; and hemoglobin, 90 per cent. The blood Wassermann reaction was negative. An electrocardiogram made on admission showed changes consistent with enlargement of the left ventricle and myocardial damage.

Course. Lumbar puncture showed frankly blood cerebrospinal fluid under an initial pressure of 240 mm. of water. The temperature on admission was 98.8°F., pulse rate 84 and respirations 30 per minute. The pulse rate became rapid and bounding when the patient developed Cheyne-Stokes respiration. The blood pressure rose to 280 systolic and 130 diastolic. Eighteen hours after admission, while the patient was being draped for a phlebotomy, she suddenly ceased to breath. Cardiac sounds continued muffled, slow, and regular although no pulse could be felt. Artificial respiration and stimulants were given without avail and the patient died.

Necropsy Findings. Brain. Gross. The leptomeninges were dry and transparent. The cerebral hemispheres appeared to have flattened sulci and gyri indicating increased

[1] The first four cases were presented in previous issues of the Journal (Vol. VIII, No. 3, 4 and 6).

intracranial pressure. The cerebral cortex was pale and of uniformly increased consistence. There was some dark reddish coagulated fluid in the cisterna magna. On severing the cord in the foramen magnum, there seemed to be slight oozing of blood from the

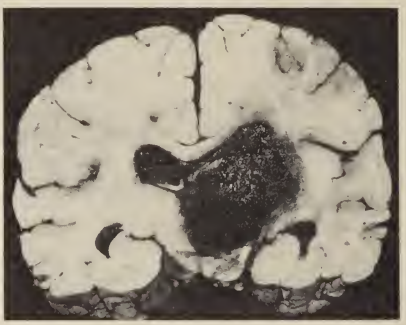


FIG. 15. Coronal section of the brain showing massive hemorrhage in the right hemisphere which had broken through into the ventricular system.

FIG. 16. Cross section showing recanalization of a thrombosed blood vessel. (Hematoxylin-Eosin, photomicrograph × 47.)

meningeal space about the cord. The basilar artery was displaced to the right of the midbrain and showed considerable arteriosclerosis. (The slight staining of the meninges at the base of the brain with blood may have been due to oozing from engorged vessels which were cut during the autopsy procedure.) The pituitary gland appeared grossly normal.

Attached to the dura over the cauda equina and corresponding to the site of lumbar puncture was a small blood clot. Blood vessels in this region of the spinal cord were engorged and the subarachnoid space was stained diffusely with bright red blood.

On coronal sections of the brain, a large hemorrhagic area was found in the region of the right thalamus, extending posteriorly into the midbrain on the same side (fig. 15). The dorsal portion of the right thalamus was almost completely replaced by blood. The blood within the thalamus communicated with blood in the parts of the adjacent lateral ventricle in the region of the posterior and descending horns.

Microscopic. Sections of the right thalamus showed a large hemorrhagic area composed of partly coagulated blood and blood pigment. In the zone surrounding this hemorrhagic area there was widespread rarefaction and degeneration of brain tissue. Many congested blood vessels with various degrees of arteriosclerosis were seen. Traversing this same area,

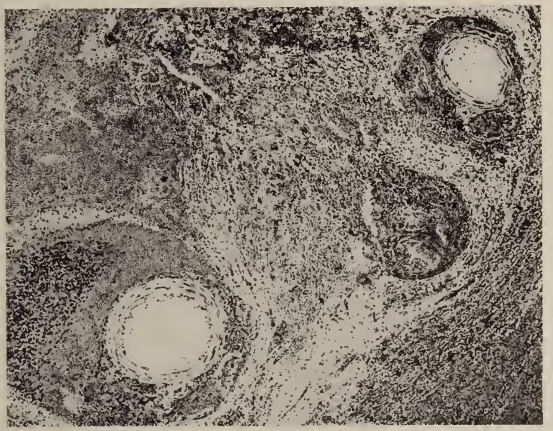


FIG. 17. A series of vessels with the larger one showing a dissecting aneurysm. (Hematoxylin-Eosin, photomierograph × 75.)

there was a thrombosed, recanalized vessel (fig. 16). Nearby, in this same area, was also seen a thrombosed, disintegrated, dissecting aneurysm (fig. 17). Changes such as those seen in the cerebral blood vessels suggested a long duration of the softening process which often precedes actual rupture of the vessels in cases of massive cerebral hemorrhage.

Sections of the midbrain showed that the hemorrhagic area, which was observed on gross examination to have extended caudally from the thalamus, had broken through a defect in the wall of the cerebral aqueduct.

The meninges were thickened and contained a small amount of free blood. The meningeal vessels were congested and their walls thickened.

In the cerebral cortex, many of the nerve cells were swollen and their nuclei had shifted to the periphery of the cell. The perineural spaces were widened. In the subcortex there was a diffuse increase in the glial nuclei with moderate perivascular mobilization of glial elements. The blood vessels both in the cortex and subcortex were congested and the perivascular spaces enlarged.

Comment. Dr. Globus. In this case, the sudden onset of symptoms and the rapid progress to a fatal termination justify the diagnosis of massive cerebral hemorrhage. The term "massive cerebral hemorrhage" suggests the explosive character of the bleeding into the brain and excludes hemorrhage due to external trauma or localized within the subarachnoid or subdural spaces. The term also excludes small or petechial hemorrhages within the brain.

This case provides additional confirmation of the results of recent investigations (1) which indicate that massive spontaneous cerebral hemorrhage is an end-result of preexisting disease of the blood vessels causing ischemia with softening. The formation of the area of softening may precede the fatal hemorrhage by years, months, days, or even by a few hours. With the sudden flooding of the softened tissue with blood under arterial presure, rapid disorganization of surrounding normal tissue takes place by means of pressure necrosis and occlusion of collateral arterioles. As a result, the ultimate size of the hemorrhage may be many times that of the original area of ischemic softening.

Thrombosed and recanalized blood vessels are frequently found in these areas. Other vessels are completely destroyed or may show splitting of their coats suggesting the appearance of a dissecting aneurysm. The hemorrhagic cavity is usually surrounded by remnants of softened brain tissue containing many congested blood vessels embedded in a mass of compound granular cells. For some distance about the area of hemorrhage there is diffuse gliosis, focal demyelinization and small areas of encephalomalacia.

Reported by *M. Kibbe, M.D.*

REFERENCE

(1) Globus, J. H.: Massive cerebral hemorrhage. Proc. A. Res. Nerv. & Ment. Dis. 48: 438, 1938.

Case 6. Tuberculous Meningitis

[*From the Neurosurgical Service of Dr. I. Cohen*]

History (Adm. 459402; P.M. 11560). A boy, aged 12 years, had three admissions to this hospital. When 6½ years old, in 1934, he entered the hospital on the fourth day of an ear infection in a state of delirium. His temperature was 103°F., his neck was moderately stiff, and there was a bilateral Kernig sign. Blood culture yielded streptococcus hemolyticus. A mastoidectomy and jugular vein ligation were carried out. He was given several transfusions and after an initial stormy postoperative course, there followed gradual recovery. However, the healing of the mastoid wound was delayed for about nine months. About one year later, in the course of an upper respiratory infection, swelling and tenderness developed in the region of the old mastoid wound. This broke open spontaneously and discharged purulent, foul-smelling material. Since then there had been a continuous discharge from the wound, requiring constant dressing. This condition brought him to the hospital for the second time (May 4, 1936). A brief period of observation showed him to be afebrile and free of pain, consequently he was returned to the Out-Patient Department for further ambulatory treatment.

He remained in apparently good health, except for an occasional cold, until seven weeks before his last admission. At that time he began to feel drowsy, developed a sore throat, and within two days his left ear canal and mastoid wound began to discharge pus again. His temperature rose to 105°F. and he became and remained delirious over a period of several days. Sulfanilamide was administered for two weeks and he seemed to improve, with his temperature dropping and continuing at a lower level. During the seventh week of the illness the ear stopped discharging and the temperature dropped to normal. He felt well enough to leave the bed and go outdoors. On the following day, however, the mastoid wound "closed," his temperature rose to 103°F., severe headache developed, and he began to vomit. He entered the hospital for the third time on July 8, 1940.

Examination. The patient was well developed, somewhat obese, with Fröhlich-like habitus. The left ear drum showed a large, anterior perforation and a small amount of exudate. The left mastoid area was neither tender nor discharging. Neurological status revealed the patient to be alert, intelligent and cooperative. The deep reflexes were equal, but slightly depressed. The right abdominal reflexes were less active than the left.

Laboratory Data. The urine showed one plus albumin. Blood: hemoblobin, 80 per cent; white blood count, 6,700; mature polymorphonuclear leucocytes, 46 per cent; immature, 11 per cent; lymphocytes, 34 per cent; monocytes, 6 per cent; eosinophiles, 1 per cent; basophiles, 2 per cent. Urea nitrogen, 7 mg. per cent; sugar, 115 mg. per cent; carbon dioxide combining power, 52.5 volumes per cent. Blood culture was negative. Widal agglutination test was negative. Mantoux test was positive, 1/100,000. Cerebrospinal fluid: Colloidal gold and Wassermann reaction were negative; globulin, plus-minus; sugar, 45 mg. per cent; total protein, 127 mg. per cent. An x-ray examination of the skull showed marked clouding of the left petrous pyramid extending to the tip, but no evidence of bony destruction. The left mastoid area showed diffuse density of the entire left peri-antral region extending into the petrous pyramid. The sella turcica was rather small.

Ventriculography performed July 10, 1940 showed "insufficient air for diagnosis." Another ventriculography performed July 16, 1940 showed "marked internal symmetrical hydrocephalus. The fourth ventricle is not seen."

Course. A lumbar puncture performed on July 7, 1940 showed the initial pressure of the cerebrospinal fluid to be 120 mm. of water. The Queckenstedt test showed no block. The cerebrospinal fluid was clear, colorless, and contained 500 cells per cu. mm. of which 94 per cent were mononuclears and 6 per cent polymorphonuclear leucocytes; sugar was 35 mg. per cent; chlorides, as sodium chloride, were 665 mg. per cent; total protein was 134 mg. per cent.

The neurological status at this time was recorded as follows: "The patient is irritable, lies on his right side, assuming a jack-knife position. The right fundus shows an indistinct nasal disc margin. The neck is stiff and pain is provoked by its flexion. There is slight dysdiadochokinesis in the right hand."

A brain abscess was suspected, but the neurosurgeon could find no definite indication for operative intervention. For the next four days headache and irritability persisted and then the patient passed into a semi-stuporous state. His temperature rose to 105°F., but the pulse rate remained as low as 70 per minute. A secondary mastoid exploration was done to rule out epidural abscess, but the dura and petrous pyramids were found to be normal. In the course of the procedure, forty cubic centimeters of fluid were removed from the left lateral ventricle and were replaced by air. Shortly thereafter projectile vomiting developed, the left arm became paretic, transient left ankle clonus appeared, the left abdominal reflexes could not be elicited, and a bilateral Babinski sign was elicited. The following day lumbar puncture was performed and cerebrospinal fluid was removed under

an enormous initial pressure of 500 mm. of water. The Pandy reaction was four plus. The fluid was clear, but contained 300 cells (all lymphocytes). In the course of the next few days repeated daily lumbar punctures showed similar findings. It was then noted that the pupils became small and the eyes assumed conjugate deviation to the right. Left hemiparesis including the face appeared; the abdominal reflexes could not be elicited; the deep reflexes on the left side became hyperactive and a left Babinski and bilateral Kernig sign

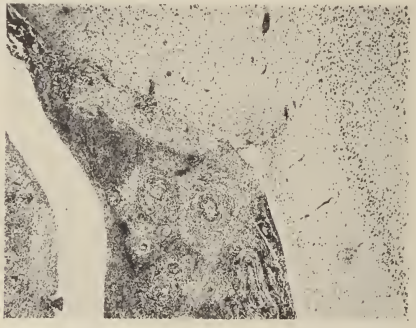


FIG. 18. Section showing advanced changes of tuberculous meningitis. (Hematoxylin-Eosin, photomicrograph × 48.)

FIG. 19. Section of oculo-motor nerve showing lymphocytic infiltration and giant cell formation. (Hematoxylin-Eosin, photomicrograph × 97.)

were present. The last two days of the patient's life were marked by a series of spasms which were described as "decerebrate fits," each lasting 30 seconds and characterized by opisthotonus, extreme extention of the legs and arms and pronation of the wrists. Air studies were repeated on the last day of the fatal illness and disclosed dilatation of the lateral and third ventricles. A trephine exploration was done in search of a probable left cerebellar abscess but yielded negative results. The patient remained in stupor, his

temperature rose, Cheyne-Stokes breathing developed, and he died on the day following the last surgical proeedure.

Necropsy Findings. Brain Gross. A large open wound was present in the left mastoid region paeked with iodoform gauze. A reeent ineision extended anterior from this for about 5 em. There were two reeent burr holes in both posterior frontal regions of the ealvaria. Similar holes were present in the dura. The meninges appeared normal. The brain weighed 1470 grams, was uniformly softened and exhibited broadening of the gyri and narrowing of the sulei. There was an extradural blood elot over the left petrous pyramid.

On seetioning, asymmetry of the ventrieles was noted. The right ventriele was somewhat eompressed and the left was somewhat enlarged. In the region of the right internal eapsule, almost through its entire length exeept for the anterior portion, there was an area of diminished eonsistenee and diseoloration. It gave the impression of an area of hemorrhagie softening. There was an area of deereased eonsistenee involving the left lentiform nueleus and the internal eapsule.

Microscopic. A seetion of frontal eortex revealed moderate infiltration of the meninges with a predominantly lymphoeytie exudate. The blood vessels were injeeted and their walls thiekened. Some vessels showed infiltration of the adventitia with mononuelear eells. Sections at the base of the brain in the region of an area of softening deseribed in the gross anatomieal findings showed a dense eellular exudate admixed with sero-fibrinous material and areas of easeation (fig. 18). There was pronouneed vascularity and the vessels exhibited marked eellular infiltration of the adventitia, splitting of the internal elastic lamina, and infiltration of the endothelium by lymphoeytes and plasma eells. The adventitia of some vessels showed areas of neerosis.

Langhans' giant eells were noted in the region of the easeation. The eellular exudate was predominantly lymphoeytie, but many polymorphonuelear leueoeytes as well as many epitheloid eells were present. The ependymal lining of the third ventriele was interrupted by ependymal granulations. There were seattered areas of eneephalitis eonsisting of perivaseular infiltration of round eells and peteehial hemorrhages in the proximity of the meningeal infiltration. Direet extension of the meningeal proeess into the brain substanee was thus seen frequently. The extension oeeurred ehiefly along the perivaseular spaees. In the eerebral eortex the pyramidal eells showed moderate degeneration. The oeulomotor nerve showed mononuelear infiltration of the perineurium and endoneurium eontaining a few giant eells (fig. 19). Seetions stained by the Ziehl-Nielson method disclosed the presenee of aeid-fast baeilli.

Reported by *B. Goldberg, M.D.*

On February 10, 1942, Dr. B. S. Oppenheimer, in celebration of his sixty-fifth birthday, was given a special volume of the Journal of The Mount Sinai Hospital dedicated to him by his colleagues, associates and friends. Dr. Eli Moschcowitz, the Chairman of the Anniversary Volume Committee, who presented the gift spoke of the high esteem in which Dr. B. S. Oppenheimer is held. Dr. Oppenheimer replied and showed his appreciation by presenting Dr. Eli Moschcowitz with a replica of the Gold-headed Cane, first carried by Dr. John Radcliffe in 1685, which after having been passed down by successive physicians, each one appointed by his predecessor, was deposited by the widow of the last possessor, Dr. Matthew Baillie in 1825 in the Royal College of Physicians, London.

Dr. Eli Moschcowitz:

"My Friends: Dr. Ben Oppenheimer:

"I feel it a privilege to be the spokesman of your thoughts upon this occasion. In various capacities, I have been closely associated with Ben Oppenheimer for over forty years, as a fellow member of the House Staff, as a fellow member of the Visiting Staff; in later years he was my Chief and throughout these epochs, he has been my frequent adviser both in the matters of policy and in the sick room. Under the most exacting tests and trials, he has never failed me. The outstanding quality that has endeared him to me is that supreme gift of self abnegation, whether in the sick room, in his hospital service, in counsel and above all, in his devotion to science, his thoughts were first of all directed to these interests and only secondarily to his own.

"But I am not here to speak of my own relations to Ben Oppenheimer. Our purpose here is to give voice to thoughts that have accumulated and motivated our minds these many years. This assemblage is made up of folk of diverse purposes and callings in life. But there is one common bond that unites us all, namely, our love, respect and admiration for Ben Oppenheimer and I am sure I voice your thoughts when I say that we welcome this opportunity to tell him, however inadequately, what we have thought of him in all these years. This tribute in not the only one we pay him today. First of all, we shall repay a debt that began when he became a member of the staff of Mount Sinai Hospital thirty-seven years ago. The obligation that this hospital owes to Ben Oppenheimer cannot be measured by a formula or mathematical equation but, certainly, we owe him much. He has stamped himself indelibly upon the history of Mount Sinai Hospital. Every hospital, in fact, all institutions of learning have a *genius loci*, or spirit of the place. Mount Sinai Hospital has a *genius loci* of its own. I cannot define it but it is there and it is one of which all of us are proud because it has kept its name high and bright in the records of the past. No one can deny that Ben Oppenheimer's contribution to this spirit

has been large. As our colleague, as our Chief, as an investigator and above all, as our teacher, he has kept the faith and the banner of Mount Sinai Hospital unsullied. But Ben Oppenheimer's service extends far beyond the confines of this Hospital and no better testimony of this fact can be cited than the wide geographical distribution of the contributors of the Anniversary Volume. These contributors are not only national, but international and had not the war intervened, the scope would have been far wider. Furthermore, no greater tribute to the esteem with which Ben Oppenheimer is regarded could be given than the scientific calibre of the majority of the contributions; he stands shoulder to shoulder with the princes of our profession.

"Dr. Oppenheimer, this volume represents our work, much of it inspired by your teaching. But in a larger sense, it is a symbol of our affection. We present it to you with the full realization that it is only a small part of what we owe you and above all, with the fond wish that this occasion does not connote the end but only the beginning of a new milestone in our association and that you may continue to be the trusted guide and the inspiration that you have been in the past."

Dr. Bernard S. Oppenheimer:

"My dear Eli, Joe Globus, Sol Silver and all you friends who have worked shoulder to shoulder to make this wonderful gift possible.

"No gift could possibly have given me greater happiness, more real satisfaction, or filled me with a deeper sense of gratitude to all who contributed toward it. As every day I turn the leaves to read them, an overwhelming compunction will cover each blessed name, as I will realize more and more how much time, work and thought have been put by all of you into this labor of love; but with all this 'a throng of comradely recollections will fill my heart' as I recall the varied experiences we have had together; the feeling of compunction will probably gradually fade away, and be replaced at least by the intention to justify in some small measure the sacrifice which all of you have made who have helped to produce this volume.

"Then there will also come the feeling and the wish to do something for each and every one of you, besides blessing you. For months I have been waiting for an opportunity to begin on my good friend, Dr. Eli Moschcowitz, whom I first learned to know at Mount Sinai in July, 1901. He has outlasted and succeeded me, and so it seems fitting just now to start a new tradition on the medical service of the Hospital by presenting him with a Gold-headed Cane, or rather a replica of the Gold-headed Cane. The original gold-headed cane was passed from the leading London internist to the next for five generations. It was first in the possession of Dr. John Radcliffe who founded the Radcliffe Infirmary, the Radcliffe Observatory at Oxford and two Travelling Fellowships; it was then passed on to Meade, to Askew who collected the Bibliothica Askeviana, to Pitcairn, and finally to Matthew Baillie, the nephew of John and William Hunter. Incidentally Baillie was the first English clinician to correlate pathology and clinical medicine in the way that led to the epoch-making work of Addison,

Bright and Hodgkin. When the use of such canes went entirely out of fashion, Mrs. Baillie, the widow of Dr. Baillie, presented it in 1825 to the then New College of Physicians where I hope it is still resting safely.

"The coat of arms of each of the five physicians was engraved upon the head of the cane, and the arms were also the vignettes which headed each of the five chapters of the book which was written about the Cane in 1827. I have been at great pains to discover the arms of the Moschcowitz family, without asking Eli directly. I could not find it, and even the College of Heraldry after painstaking search failed to find the device. So I have ventured to devise one myself for Eli; it consists of a heart as big as a house, and a brain in proportion.

"So much for the gold head; but there remains the stout staff. As you are still youthful and childlike, Eli, at present you will not lean upon the staff, but will carry the cane jauntily in your hand, but as you get older and perhaps even grow a white beard, you may find it more comfortable to lean on your staff, but never too heavily, and I can promise you that the staff of Mount Sinai will never, never fail you. It will never fail you, and by the same same token it will never fail our country.—I have the privilege of presenting you with a new gold-headed cane."

THE STORY OF THE MOUNT SINAI HOSPITAL

The first of a series of installments of the story of The Mount Sinai Hospital appeared in the March issue of the JOURNAL. *Offered in celebration of the Hospital's ninetieth birthday, these historical notations in a way reflect the course of medicine in New York and elsewhere since 1852, as well as the changing environment. The narrative has been compiled by Miss Jane Benedict from hospital archives, personal and professional correspondence, medical and historical literature, and extensive interviews with those who have been both eye-witnesses and agents of its progress. It is presented, not as a definitive history of the Hospital, but rather as source material from which a more complete history is to be written later. Corrections are welcome if errors of fact or interpretation are discovered.**

The first installment described the founding of the Hospital and depicted its founders. It sketched the social factors which made such an organization a needed addition to old New York.

This installment continues the narrative from the time ground was broken for Mount Sinai's first home, the laying of the cornerstone, to the dedication ceremony. It gives a brief account of how and from whom support was obtained, with a glimpse of New York at that period.

THE FORMATIVE YEARS, 1852–1872

II

Ground was broken for Mount Sinai's first home in the fall of 1853. On October 30, the Building Committee reported that in ten days the mason would be ready for the laying of the cornerstone. It was not until Thanksgiving Day, however, that the ceremony took place.

Invitations were sent to the "President, Trustees, and Hazanim (Cantors) of the several Hebrew Congregations in this City and vicinity; also the President, Directors and other Officers of the various Hebrew Charitable Societies"; to members and subscribers of the Hospital Society, and to other interested persons. Guests were asked "to meet the Officers and Directors at the . . . Synagogue in Crosby Street on Thursday, November 24, at 2 o'clock p.m. for the purpose of proceeding to lay the cornerstone of the Institution."[23]

The minutes record that the Board and their guests "having formed in procession, proceeded by cars of the 8th Avenue Railroad at Canal Street to the ground in 28th Street."[24] The "Railroad" by which they "proceeded" was horse-drawn, with cars pulled on tracks, an innovation which had been introduced into New York twenty-one years earlier and was not to be superseded for another ten years.

"The trowel having been presented by H. Hendricks, Esq. (Treasr.) chairman of the Building Committee with appropriate remarks, was received by the

* Additional information which may help to make the picture more complete will be appreciated and may be addressed to the Historian of the Hospital.

[23] Minutes of Board of Directors' Meetings, Jews' Hospital, November 14, 1853.

[24] Minutes of Board of Directors' Meetings, Jews' Hospital, November 24, 1853.

President S. Simson, Esq. who replying thereto proceeded to lay the cornerstone. Services were also performed by the Revs. J. J. Lyons, S. M. Isaacs, and Ansel Leo. The Board . . . subsequently attended the delivery of a Discourse by the Rev. S. M. Isaacs at the Wooster St. Synagogue. . . ."[25]

By December, 1853, it was announced that the Hospital building had reached the height of one story, that the contracts let amounted to nine thousand dollars and that at least two thousand dollars more was needed to meet that commitment. In order to raise this sum of money a "Dinner and Ball" was given in January of 1854, to which the committee decided that "ladies, as well as gentlemen, should be invited, well persuaded that in enlisting the sympathies of the gentler sex, their cooperation in so noble a cause could not fail to crown it with complete success."[26]

This fund-raising event also marked the celebration of the laying of the cornerstone. It was held at Niblo's on the corner of Prince Street and Broadway, a garden and restaurant where the finest social functions of the day were held. "A very large and respectable company, composed of Israelites, and our fellow citizens of other denominations, assembled in the large reception room." At five o'clock, "after sufficient time had been allowed for friendly greetings, and an introduction to the venerable President of the Institution, they were ushered into the spacious banqueting-room, which had been arranged for their reception and entertainment; sixteen tables were spread . . . . The usual prayers, before and after meat, were performed by the Rev. J. J. Lyons, and Rev. Ansel Leo, after which the President stated in a brief speech the objects and requirements of the Institution. Toasts, as usual, appropriate to the occasion, were read, and addresses delivered . . . ." After the meal and the formalities had been completed, "the company withdrew to the splendid ballroom" to dance the quadrille, polka, schottische, and waltz.[27]

The fund raising, however, was by no means forgotten amid the abundant festivity. Donations amounted to seven thousand, two hundred and thirty-five dollars. Again a closely knit group rallied to support the Hospital, and names already prominent in its brief history are foremost among the donors. The Directors are listed among the first: Sampson Simson, Henry Hendricks, John I. Hart, John D. Phillips, Benjamin Nathan, John M. Davies, Theodore J. Seixas, Rev. S. M. Isaacs, and Isaac Phillips. The sons of two of these men, Lewis Phillips and Isaac Hendricks, seconded their fathers in helping the new institution. Miss Selina Hendricks, among others, demonstrated tangibly the "sympathies of the gentler sex." Emanuel B. Hart, who in 1857 was to be elected a Director and was later to be President of the Hospital, Lewis M. Morrison, and Joseph Fatman, are all included in the "Report and List of Donations." Henry I. Hart, chairman of the committee which gave the "Banquet and Ball", was joined by others of its members: Henry Josephi, Jacob I. Moses,

[25] See footnote 24.

[26] Report and List of Donations, Banquet in Aid of Funds of Jews' Hospital, January 26, 1854.

[27] See footnote 26.

George S. Mawson, Dr. Simeon Abrahams. Five men who had been on the Young Men's Committee of two years before again gave assistance. They were Barrow Benrimo, George Henriques, Adolphus S. Solomons, Rowland Davies, and L. Bierhoff. The names of Rev. and Mrs. Ansel Leo, relatives of Sampson Simson, and of Rev. J. J. Lyons of the Portuguese Congregation, again appear among the sponsors.

The long list of almost five hundred contributors on this single occasion also contains names which indicate that the efforts of the founders and their associates had aroused the sympathies of many benevolent outsiders, such names as O'Brien, Campbell, Gilsey, Weeks, Jewett. Donations came from Philadelphia, Schenectady, Charleston, Baltimore, New Orleans, and Chattanooga; for the development of railroads and the extension of the telegraph system six years before had shortened distances and cities were brought closer together. Of particular interest is the contribution of Dr. William B. McCready, a leading New York Physician and a founder of the New York Academy of Medicine (1847), who was to become one of the Consulting Physicians to the Hospital when it opened the following year. The circle of those interested in the Hospital was widening.

A few weeks after the "Banquet and Ball" the Board received news of the generous legacy of twenty thousand dollars willed to the Hospital by Judah Touro, a wealthy philanthropist of New Orleans. Judah Touro had been a native of Newport, Rhode Island, and a prominent member of its Jewish community, originally settled by some of the Jews who had landed in New Amsterdam in 1654. They arrived in the "new land" penniless and Peter Stuyvesant ordered their baggage sold at auction in order to provide payment for their passage. Moreover, two of their number were put into jail as "hostages." Discouraged by such a reception, some of the band trudged on to Newport, there to found the thriving Jewish colony.[28] It was this colony young Judah Touro left when he sailed for New Orleans in 1802. He opened a small shop on the waterfront where he sold New England products—codfish, candles, soap, and cheese. His wares were well received; he prospered, and entered the shipping business, building up a tremendous fortune. Touro exhibited benevolent inclinations early and throughout his life was a large contributor to charitable and public funds and religious enterprises, both Jewish and Christian. A fortune of eighty thousand dollars was left to him when his sister died, but he resigned all legal title to it, turning it over to charity. In his own will he left numerous bequests to charitable and public institutions, distributing his gifts beyond his native Newport and his adopted New Orleans.[29]

With the impetus given to the Hospital funds by the success of the "Banquet and Ball" collection and by the encouraging news of the Touro bequest, the Directors turned their attention to the acquisition of more land. Sampson Simson had given the Hospital one lot and had set aside the adjoining one for the

[28] Wilson, James Grant: Memorial History of the City of New York. New York History Company, Vol. 4, 1893.

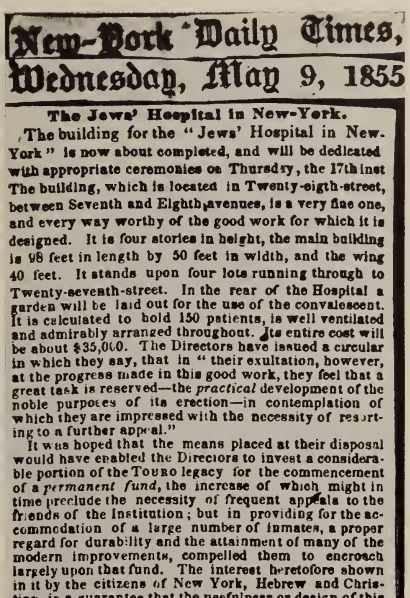
[29] Renshaw, James A.: Judah Touro, Louisiana Quarterly, Vol. 11, 1928.

erection of an "Orphan and Indigent Asylum." The Hospital, however, was apparently given the use of the second lot for a garden, although the Asylum continued to be mentioned as a future project. The second annual report, dated December 31, 1854, indicates that the Hospital had bought two lots of land "extending from 27th to 28th Streets, with a front on each street of 25 feet, and situated on the easterly side of, and immediately adjoining the lots donated by the President of this society. . . . The acquisition of these lots enabled the Directors to alter the original plans for the Hospital building, so as to occupy a front of 50 feet on 28th Street; the lots in the rear, being those fronting on 27th Street, to remain open until otherwise required, so as to afford ample space for air and exercise." In reporting this to their membership, "the Directors . . . experience much satisfaction at the progress made within the last year . . . .This result thus far, is mainly attributable to the unprecedented success which attended the Banquet celebration of the 26th of January last." The Touro bequest had not yet been received, "although the Directors are in daily expectation of receiving the amount of the legacy. . . . " Indeed, the minutes show that the month previous to the report, the Directors had signed notes amounting to five thousand dollars to meet the cost of construction. The building was nearly completed, however, and the report goes on to note that "arrangements are being made for furnishing the *interior*, and the building itself, it is contemplated, will be entirely finished within the next sixty days." It is interesting to note that this early report bears the imprint "Adolphus S. Solomons—Print." The young man who, during his German tour in 1851, had felt deep shame in admitting that there was no Jewish hospital in the United States, had by now established his own publishing house and was able to offer its services as well as his own efforts toward putting into effect his resolve that "such a reproach upon his native land should not long exist."

In February of 1855 Sampson Simson, now seventy-five years old, resigned as President, sending his fellow members of the Board "my fervent wishes for prosperity of the institution and your individual happiness." Despite the entreaties of a committee which was appointed to persuade him to alter his decision, the elderly founder held firm in his determination. The Directors elected John I. Hart as President, with Benjamin Nathan as Vice-President and Theodore J. Seixas as Secretary. Henry Hendricks remained Treasurer. These elections took place in February of 1855, at the first meeting to be held in the Hospital building. A resolution of thanks was sent to the Portuguese Congregation for allowing the Board to meet in its synagogue during the previous three years.

On May 17, 1855, the building on 28th Street was thrown open to the public and dedicated. The service was a religious one, such as was used in the dedication of a synagogue—a fact which drew unfavorable comment from Isaac Leeser, editor of one of the Jewish papers, The Occident. The invitation to this "peculiarly interesting occasion, the first of this character to be recorded in the annals of our American-Jewish population," lists as chairman of the committee George Henriques of the Young Men's Committee, and as secretaries three who had

served with him: Adolphus S. Solomons, Samuel A. Lewis, and Barrow Benrimo. Many familiar names form the body of the committee: Sampson Simson, the retired President who still continued to be moderately active in the Hospital's affairs; Isaac Hendricks, the son of Henry Hendricks; Emanuel B. Hart; L. H. Simpson of the Young Men's Committee; Asher Kurscheedt, Dr. Simeon Abra-



New-York Daily Times,
Wednesday, May 9, 1855

The Jews' Hospital in New-York.

The building for the "Jews' Hospital in New-York" is now about completed, and will be dedicated with appropriate ceremonies on Thursday, the 17th inst The building, which is located in Twenty-eighth-street, between Seventh and Eighth avenues, is a very fine one, and every way worthy of the good work for which it is designed. It is four stories in height, the main building is 98 feet in length by 50 feet in width, and the wing 40 feet. It stands upon four lots running through to Twenty-seventh-street. In the rear of the Hospital a garden will be laid out for the use of the convalescent. It is calculated to hold 150 patients, is well ventilated and admirably arranged throughout. Its entire cost will be about $35,000. The Directors have issued a circular in which they say, that in "their exultation, however, at the progress made in this good work, they feel that a great task is reserved—the *practical* development of the noble purposes of its erection—in contemplation of which they are impressed with the necessity of resorting to a further appeal."

It was hoped that the means placed at their disposal would have enabled the Directors to invest a considerable portion of the Touro legacy for the commencement of a *permanent fund*, the increase of which might in time preclude the necessity of frequent appeals to the friends of the Institution; but in providing for the accommodation of a large number of inmates, a proper regard for durability and the attainment of many of the modern improvements, compelled them to encroach largely upon that fund. The interest heretofore shown in it by the citizens of New York, Hebrew and Christian, is a guarantee that the usefulness or design of this most worthy charity will not in any way be impaired by reason of a scarcity of the requisite funds. The gratuitous services of several eminent members of the faculty of medicine and surgery have been already tendered to the Institution.

FIG. 1. Reproduction of a column which appeared in the New York Daily Times

hams, and George S. Mawson, members of the committee for the laying of the cornerstone.

Services were conducted by Rev. J. J. Lyons and Rev. Ansel Leo. At the "Banquet and Ball" which followed, two of the speakers were Lieutenant-Governor Henry Jarvis Raymond and Israel Moses, Assistant Surgeon of the United States Army, soon to serve on the Jews' Hospital staff as an Attending Surgeon. It was announced that although it had been hoped to set aside part of

the Touro legacy as a permanent fund, it had become necessary to use all but five thousand dollars of it in meeting the cost of building the hospital which reached the sum of thirty thousand dollars. Once more an appeal was made to the public, and donations amounting to six thousand dollars were subscribed. The banquet included the drinking of twelve toasts, beginning with one to the Jews' Hospital and ending with the traditional "To the Ladies."

The building was opened to public inspection; it was four stories high, with a large ward and several small ones on each floor. In the basement were the kitchens, offices, and utility closets. A contemporary account reveals that "the ward . . . contained a number of bedsteads, near each of which stood an arm-chair . . . . Everything looked scrupulously clean and white . . . . For ventilation

Fig. 2. A drawing of the Jews' Hospital, later renamed The Mount Sinai Hospital

ample care had been taken, by having in every story openings, covered with metallic gratings, from the outside, so that pure air will always flow in, no matter what the state of the weather may be: we believe also that the draft through these openings can be stopped off should it prove too strong, as we felt during the ceremony of dedication . . . ." The account finds it worthy of comment that "water and gas are introduced."[30] The Croton water system had been completed thirteen years before the Hospital opened, but the Board minutes indicate that its use had to be paid for although the Directors had petitioned the Common Council to relieve them of this expense.[31] The editor of The Occident notes that

[30] An Account of the Dedication of the Jews' Hospital, The Occident, Isaac Leeser, Editor, July, 1855.

[31] Minutes of Board of Directors' Meetings, Jews' Hospital, February 4, 1855; November 11, 1855.

in a small building behind the Hospital "there are separate rooms for pay patients."[32] He remarks also that "the ladies of New York must not be forgotten in this connection, as they for weeks before the opening of the hospital were engaged in preparing the bedding and other things of the kind, in ample and we should judge abundant quantites."

FIG. 3. Rachel, the great French tragedienne

The year the Hospital opened, 1855, the notorious and corrupt Fernando Wood was Mayor of New York. He was re-elected in 1856 and again in 1857—the year he particularly distinguished himself by defying the State Government. The Legislature had passed amendments to the City's charter, one of which provided for a uniformed and more efficient police force, known as the Metro-

[32] See footnote 30.

politan. The incumbent police force were Fernando Wood's political adherents. Arming this band, he withdrew into the City Hall and barricaded the building. Branding the amendment unconstitutional, he "defended" the City Hall from the Governor's representative, Street Commissioner Daniel D. Conover. Finally, however, the Seventh Regiment and two warrants of arrest with which Daniel Conover was armed persuaded him to leave his fortifications. The following year (1858) Wood was defeated by the candidate of a Citizen's Committee, Daniel T. Tiemann, who was elected on a platform of reform. Tiemann was re-elected in 1859, but because of a split in the Citizens' Committee, Wood was back in office in 1860 and was re-elected in 1861. Bribery and corruption were reinstated, to stay for a good many years.[33]

Even before 1852 New York had begun to take on the cosmopolitan aspect with which we are familiar today. In 1850 Jenny Lind, the "Swedish Nightingale," had been a triumphant success under the managership of Phineas T. Barnum. She had sung at Castle Garden, the center for all public entertainment. In 1851 Louis Kossuth, the Hungarian patriot, had been enthusiastically acclaimed in the same building.[34] The year after the Hospital's incorporation, on July 4, 1853, the first World's Fair to be held in the United States opened in the Crystal Palace, a large iron and glass structure which, until it burned down five years later, was the wonder of its day. In 1855 the great French tragedienne, Rachel, toured the country. In New York she was waited upon by a committee from the Jews' Hospital; she expressed her interest by sending a donation of one hundred dollars to the institution.[35] In the same year William Makepeace Thackeray delivered a series of lectures.

In August of 1858 the possibility of closer contact with other continents was to be made a reality, when the first cable was laid across the Atlantic and messages were transmitted over it. It broke, but was finally relaid in 1866. In 1859 the largest streamship afloat, the Great Eastern, the Queen Mary of her time, crossed the ocean in eleven days. That same year the Japanese Embassy was established, seven years after Commodore Perry had visited Japan, and its staff was feted in New York with great ceremony.[36]

The new hospital was born into a world in which geographical distances were shrinking as horizons continued to expand.

The next installment will picture the medical background and give a brief account of the contemporary nursing practices, the first Medical Staff of the Hospital, and the organization and facilities with which it began to serve the community.

[33] Wilson, James Grant: Memorial History of the City of New York. New York History Company, Vol. 4, 1893.

[34] See footnote 33.

[35] Minutes of Board of Directors' Meetings, Jews' Hospital, September 2, 1855; November 4, 1855.

[36] Wilson, James Grant: Memorial History of the City of New York, New York History Company, Vol. 4, 1893.

David H. Davison

October 11, 1854–November 22, 1941

With the death of Dr. David H. Davison there passes an interne, who for many years has headed the list of living Mount Sinai Hospital graduates. Dr. Davison started his training here immediately after his graduation from the College of Physicians and Surgeons, Columbia University in 1876. He served as an interne for two years, was on the Dispensary staff of the Children's Department until 1882, served as Admitting Physician for the long period of fifteen years—from 1883 until 1898. He was Adjunct Attending Physician the next year until 1910, became Associate Attending Physician in 1911, and remained in that position until his resignation in 1919.

Part of the time it was my good fortune to serve under him, and thus I had abundant opportunity to recognize and appreciate his exceptional ability as a diagnostician, especially in one so young. This was exemplified for the most part in the field of physical diagnosis, and I have often wondered whether his skill in this department of medicine may not have been due in large part to his violin playing. His playing on this instrument bordered on the professional, and must have developed a highly sensitive touch and ear. I know in my own case, I have, as a physician, been grateful for my years of performing at the piano. It was a real joy, for such of us as were musical, to listen at the door when he was faithfully practising a Beethoven or a Mendelsohn concerto. He was very fine also in chamber music and many a delightful hour did I enjoy playing with him during our spare time. As an interne I had quietly slipped a rented piano into my room. I never asked for permission, and apparently no one in authority disapproved. When I last visited Dr. Davison at his home he reminded me that this course was pursued at his suggestion. We played trios with the help of a cellist from outside the hospital. I recall with a good deal of amusement (into which steals a certain amount of satisfaction) what took place one morning at the bedside of an old quartermaster who was a good deal of a wag. Enquiring as to the kind of night he had passed, he replied, "Well, Doctor, being a warm night, the windows of your room and of the ward were open and I heard your music." Somewhat self-conscious that perhaps we had disturbed him, I was delighted to have him continue, "Well, Doctor, your music did me more good than all your medicines."

Dr. Davison served in those pre-bacterial and pre-laboratory days when only the simplest urine and blood tests were in vogue. It will seem almost incredible to the young interne of today that at that period of which I speak there was not even a sputum examination for tubercle bacilli or a blood test for plasmodia, or even a smear for gonococci. Differential blood counts were, of course, out of the question and we went on the roughest estimates of the number of leucocytes. It would seem today like a pretty severe handicap for a young beginner, and I could mention many more. All these "crutches" in making diagnoses are so completely taken for granted today, that some of our young internes may not even suspect how fortunate they are!

I must add a word of praise for Dr. Davison's great patience and kindness to all patients. He never failed to show the due regard of a true gentleman towards those who were doubly afflicted with both illness and poverty.

After leaving the hospital Dr. Davison became a general practitioner and through his marriage to a sister of Daniel Frohman, most beloved of producers, ever ready to lend a helping hand to every member of the acting profession, he had a large clientele among actors. Several of his sons saw active service in the first World War and Mrs. Davison was the "Angel Mother," who entertained our soldiers in France.

Alfred Meyer

Joseph Brettauer

September 9, 1863–December 26, 1941

In the death of Dr. Joseph Brettauer, the staff of The Mount Sinai Hospital loses a valued colleague. He was associated with the hospital from 1893 until his death. In 1893 he was appointed adjunct gynecologist; in 1903, attending gynecologist; in 1925, consulting gynecologist. Throughout these forty-eight years he exerted an important influence through his decisive personality, magnetism, fearlessness and honesty.

Dr. Brettauer was born in Hohenems in the Austrian Tyrol, received his college education at Feldkirchen, was graduated in medicine at Gratz in 1887. There he was assistant to Woelfler for two years. His training in gynecology and obstetrics was obtained at Breizky's Clinic in Vienna.

Embarking on a tour of the world, he stopped off at New York and shortly thereafter married Blanche Kohn. From then on he settled in this city.

At Mount Sinai, his first assignment was to develop a gynecological outpatient department, a task which he accomplished with signal success. In 1903 he succeeded Dr. Paul F. Mundé. For twenty-two years he was in charge of a gynecological service, a model of its kind, to which he devoted unstinting energy. Brettauer was known for his keen clinical insight, his brilliant and rapid operative technic, and his conservativeness in therapy. At the outset he had the advantage over many specialists of that day in having received a thorough training in general surgery and pathology. Although he wrote little and spoke less, his influence was widespread, not only at the hospital, but also in this city, as well as throughout the country. During the many years of his incumbency, he trained innumerable men in gynecology, all of whom remember him with affectionate regard. They recall their first trembling encounter with this seemingly stern disciplinarian who yet was kindly and understanding. Most of them spoke of him as "Uncle Joe" and will continue to think of him by that name when they recall the many anecdotes based upon his disregard of formality.

Dr. Brettauer was connected with many medical societies, was the past president of the New York Obstetric Society and of the American Gynecological Society. Those of us who were associated with him, will miss his wise counsel and balanced judgment.

Robert T. Frank

ABSTRACTS

Authors' Abstracts of Papers Published Elsewhere by Members of The Mount Sinai Hospital Staff

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

A Case of Postoperative Pelvic Enterocele and Uterine Prolapse. R. T. Frank and R. Colp. Surgery, 9: 94, January 1941.

A patient who had suffered for nineteen years from severe colitis was operated upon for carcinoma of the sigmoid, in three stages. During the last stage, hysterectomy was required to remove a large fibroid blocking the pelvis.

Following complete resection of the rectosigmoid, a huge perineal traumatic enterocele complicated by eversion of the vagina and prolapse of the cervical stump resulted. Three further perineal operations were necessary in order to hold back the enterocele. This was accomplished by union of the stumps of the levators, and later a Manchester operation, but as a final stage, the sixth operation consisted of colpectomy. The patient is now apparently cured, removal of the carcinoma dating back to 1936, and completion of the repair to 1938.

The Use of Physically Induced Pyrexia and Chemotherapy in the Treatment of Subacute Bacterial Endocarditis. W. Bierman and G. Baehr. J. A. M. A., 116: 292, January 1941.

Our experience would indicate that physically induced pyrexia enhances the value of chemotherapy in the treatment of subacute bacterial endocarditis. Of two cases reported, one was due to Streptococcus viridans and one to B. influenzae, in which recovery occurred and the patients have been well for two years and for ten months respectively. A third patient, with Streptococcus viridans endocarditis, has been well for four months, but this interval is still too brief to describe as a cure.

Sulfapyridine Therapy in Lobar Pneumonia Associated with Leukopenia. C. K. Friedberg. J. A. M. A. 116: 270, January 1941.

Two cases of acute lobar pneumonia are reported, in which the white blood cell count was 700 and 2,900 per cu. mm. respectively.

In both cases multiple lobes were involved and associated with marked bacteremia. The clinical condition appeared desperate even after the use of huge doses of type-specific anti-pneumococcic serum. Sulfapyridine was administered in spite of the leucopenia and was followed by prompt improvement in the clinical picture. The leucocyte count rose progressively, and in one case reached 58,000 per cu. mm. before returning to normal.

The author concludes that the presence of leucopenia in cases of acute lobar pneumonia does not contraindicate the administration of sulfapyridine. In fact, when lobar pneumonia is associated with leucopenia sulfapyridine therapy is especially indicated, because such cases usually represent severe pneumococcic infection with a relatively high mortality.

Surgical Treatment of Intractable Ulcerative Colitis. J. H. Garlock. Ann. Surg. 113: 2, January 1941.

The author reports a series of 25 cases of ulcerative colitis treated by radical surgical methods. In 15 patients, ileostomy was performed with 2 deaths, a mortality of 13.3 per cent. In the remaining 13 cases, resection of the involved colon was later carried out. In 10 patients on whom ileostomy was not performed, short-circuiting operations and resec-

tions of the involved colon were performed. The total mortality for the entire group was 20 per cent. It is the author's opinion on the basis of this experience that surgical treatment of intractable ulcerative colitis will soon be generally recognized as the only method at our disposal of restoring some of these handicapped patients to a relatively normal existence.

Psychodynamic Factors in Illegitimacy. J. Kasanin and S. Handschin. Am. J. Orthopsychiat., 11: 66, January 1941.

This study is an attempt to elucidate further the psychologic factors in illegitimacy. It is based on a specially selected group of 16 unmarried mothers, 7 of whom had more than one illegitimate child. The group consisted of girls who were neither psychotic nor feeble-minded; they came from average American homes, presenting no striking economic or social pathology; they were all white and native born.

As a group, these patients showed extreme lack of interest in their pregnancies, a peculiarly bland affect, no desire to marry the putative fathers of the children, with frequent amnesia as to who the fathers were, or the circumstances surrounding pregnancy. At the same time, these girls were not promiscuous; had comparatively little interest in sex, and were frigid in sex relations. They showed strong attachment to their own families, with a good deal of affection for their fathers. The men responsible for their pregnancies were frequently much older than the patients.

On the basis of these data, and especially the fact that pregnancy and the birth of the child seem to be set quite apart from the rest of the girl's personality and interest, the authors offer the hypothesis that these pregnancies represent hysterical dissociation states in which the girls act out their incest phantasies as an expression of the Oedipus situation.

The authors also suggest that in such cases no especial effort be made to make it possible for the child to remain with the mother since the child does not necessarily mean the same thing to her as it does to the average mother.

Various ramifications of the problem of feminine sexuality in connection with illegitimacy are discussed. The fact is stressed that early attitudes regarding the father, especially if he is missing, and a history of promiscuity or illegitimacy in the mother's family, no matter how indefinite it may have been, play an important part in the psychologic structure of the future unmarried mother.

The Treatment of Subacute Bacterial Endocarditis. S. S. Lichtman and W. Bierman. J. A. M. A. 116: 286, January 1941.

Two hundred cases of subacute bacterial endocarditis due to Streptococcus viridans and non-hemolyticus treated with the sulfonamide drugs were collected from the literature and from the records of The Mount Sinai Hospital, and analyzed for the incidence of recovery. The results in this group of cases were compared with those in a series of 43 patients treated by combined chemotherapy and heparin, 24 patients treated by combined chemotherapy and physically induced hyperthermia and 21 patients treated by combined chemotherapy and hyperthermia induced by intravenous typhoid-paratyphoid vaccine.

It was concluded that although the series was still too small to permit an accurate statistical estimate of the incidence of recovery in these group, a consistent trend was nevertheless apparent. The *combined methods* of treatment yielded a greater incidence of recovery (11.5, 16.0 and 25 per cent respectively) as compared with a 6.0 per cent incidence of recovery in patients treated with the sulfonamide drugs alone.

Premonitory Symptoms of Acute Coronary Occlusion; A Study of 260 Cases. A. M. Master, S. Dack, and H. L. Jaffe. Ann. Int. Med. 14: 1155, January 1941.

Premonitory symptoms were present in 44.2 per cent of 260 patients with acute coronary occlusion. In most cases they consisted of substernal or precordial pain or discomfort. Other prodromes were fatigue, weakness, gastric distress, dyspnea, palpitation, nervousness, and dizziness. The sudden appearance of a typical anginal syndrome or the sudden

acceleration of a previously existing anginal syndrome frequently preceded the attack of occlusion.

The premonitory symptons usually appeared within 24 hours prior to the acute attack, but in some cases they began two or three weeks before. Their duration varied from a few minutes to several hours. Although the premonitory pain was usually either intermittent or continuous, a pain-free period frequently intervened before the onset of acute occlusion. The onset of premonitory symptoms occurred during rest in 28.5 per cent of the cases, during mild or moderate activity or walking in 68.5 per cent, and during strenuous effort in 2.9 per cent.

Premonitory symptoms were not associated with clinical evidence of myocardial infarction. Fever, leucocytosis, tachycardia, drop in blood pressure and characteristic electrocardiographic changes were absent. These factors are significant in the differential diagnosis.

The anatomic basis for the premonitory symptons is assumed to be a gradual occlusion of the lumen of the coronary artery by progressive or recurrent intramural hemorrhage or by primary thrombosis on a plaque, which may take hours or days for completion. The initiation and progression of coronary occlusion occur irrespective of physical activity or its lack. However, the coronary insufficiency and myocardial ischemia which may ensue may result in precordial pain, which is often brought on or intensified by effort.

Early recognition of the premonitory symptons with prompt institution of bed rest should lead to a reduction of heart failure and decrease in the mortality rate, even though it will probably not prevent the impending occlusion.

Necrosis of the Cornea Due to Vitamin A Deficiency. K. Schlivek and H. K. Goldberg. Arch. Opthal. 25: 122, January 1941.

A case of a necrosis of the cornea due to vitamin A deficiency is reported.

The patient was a twenty-three year old white woman who suffered from ulcerative colitis for one year. During an acute exacerbation of her illness she developed a corneal ulcer. Adescemetocele formed and soon perforated so that aqueous humor escaped and the anterior chamber was obliterated. Coincident with the necrosis of the cornea the general condition of the patient became critical. Although she had been receiving 200,000 units of vitamin A by mouth daily, the vitamin A blood level was found to be low. She was given 100,000 units of vitamin A intramuscularly on three successive days. On the third day her general physicial condition and the condition of the eye began to show marked improvement. The cornea no longer stained with fluorescein, the anterior chamber was seen to have reformed and the corneal defect had become covered with scar tissue. The vision soon returned to normal and the patient made an extremely rapid recovery.

Emphasis is placed on the fact that even when large doses of vitamins are given orally, absorption may be faulty so that in extreme cases parenteral administration is imperative. The determination of the blood level of vitamin A provides an effective laboratory method of determining the existence of vitamin A deficiency.

Absolute Muscle Power. The Internal Kinesiology of Muscle. A. M. Arkin. Arch. Surg. 42: 395–410, February 1941.

The portion of the length-tension curves of various muscles which is involved in the physiologic range of muscular activity in life was determined in experimental animals and found to be constant. The maximum work done in a physiologic contraction is proportional to the weight of muscle tissue and this relationship is constant; it may be expressed $\frac{\text{Force (Kg)} \times \text{Range (cm)}}{\text{Weight (gm.)}} = 1.2$. When the range is changed as in tendon transplants or tendon lengthenings the internal structure of muscle fibers becomes rearranged so that the original relationship of maximum work done in a contraction to weight is re-established. The practical implications of these conclusions are suggested.

Are Results of Gonadotropic Assay Performed on the Intact Immature Rat Valid? R. T. Frank and R. L. Berman. Endocrinology. 28: 211, February 1941.

Two groups of immature rats were injected each with equivalents of 40 cc. of urinary gonadotropic extract obtained from a surgically castrated woman. The first group was primed with ascending doses of estrogen (Progynon-B), 48 hours before beginning injections with gonadotropic material. The second group of animals received identical doses of estrogen simultaneously with the gonadotropic urine factor. In the "primed" group, there was a 46 per cent increase in luteinization over the control group. There was no significant increase in luteinization in the "simultaneous" group above the percentage obtained in a control group injected with gonadotropic extract only. From these experiments, the conclusion is drawn that the results obtained with intact immature rats by means of gonadotropic extract containing both follicle stimulating and luteinizing factors, may be accepted as valid.

Massive Dose Chemotherapy by the Intravenous Drip Method. H. T. Hyman. Bull. New York Acad. Med. 17: 135, February 1941.

The history of intravenous therapy dates to the first use of this method by Robert Boyle, the physicist, and Christopher Wren, the architect in 1665 following the discovery by William Harvey of the circulation of the blood.

The advantages and disadvantages of intravenous therapy are summarized. The latter were particularly of importance to clinicians since reactions were irregular and unpredictable.

In 1888 Rudolph Matas of New Orleans made the clinical observation that reactions were related to the speed of injection. It was not until 1931 that the author and his colleagues demonstrated clearly the syndrome and pathogenesis of "speed shock" and the obvious advantages of the "intravenous drip."

Since that time the intravenous drip has been universally adopted throughout the world. All commercial sets are provided with a drip. The majority, if not all, well equipped hospitals give intravenous infusions and transfusions by the drip method.

Since the original clinical work at The Mount Sinai Hospital in 1931 the intravenous drip has been used for infusions, indirect transfusions, intravenous chemotherapy with the sulfonamides and, most successfully, in massive dose arsenotherapy of syphilis.

Androgen Therapy in the Human Female. S. H. Geist, U. J. Salmon and E. C. Hamblen. J. Clin. Endocrin. 1: 154, February 1941.

The therapeutic use of androgens for gynecological disorders is the outgrowth of the observations of biochemists, physiologists and clinicians concerning the presence and rôle of androgens normally occurring in the female.

It has been shown that androgens will inhibit the pituitary and ovary and supress menstrutation. It will also cause regression and prevent cyclical changes in the endometrium. It will cause regression of the normal vaginal smear and will inhibit the motility of the myometrium and tubes. Because of these biological activities, androgens have been utilized in the treatment of functional uterine bleeding, dysmenorrhea, premenstrual mastalgia and premenstrual tension. The clinical relief of symptoms has often been striking in some types of menopause. Caution must be urged in the use of androgens in gynecological disorders. If the therapeutic dose is grossly exceeded arrhenomimetic symptoms may be produced; these, however, regress following cessation of treatment. The androgens apparently have a rational place in the therapy of certain gynecological disorders of endrocrinopathic origin. There seems to be a clear cut rationale for its use. The future, however, must assign the definite position to be occupied by androgen therapy in the female.

Relation of Tonsillectomy and of Adenoidectomy to the Incidence of Poliomyelitis with Special Reference to the Bulbar Form. A. E. Fischer. Am. J. Dis. Child 61: 306, February 1941.

The 1937 Toronto epidemic of poliomyelitis furnished an excellent opportunity to confirm and to enlarge upon previous work on the same subject. (Am. J. Dis. Child. 56: 778, October 1938). It was found among children between the ages of three and twelve years that acute poliomyelitis developed more often in those recently tonsillectomized than in others, and this increased incidence was composed entirely of cases of the bulbar form of the disease. This study also showed that the bulbar form of poliomyelitis was more than twice as common in patients who had had a tonsillectomy and adenoidectomy at any time in the past as compared to those cases whose tonsils were intact. The study confirms previous data which indicated that the tonsillo-pharyngeal area is one of the portals of entry of the poliomyelitis virus, and that the tonsils and adenoids may serve as a barrier. When this is disturbed, patients in whom poliomyelitis develops are more likely to develop the bulbar form of the disease.

The Surgical Treatment, by Drainage, of Subacute and Chronic Putrid Abscess of the Lung. H. Neuhof, A. S. W. Touroff and A. H. Aufses. Ann. Surg. 113: 209, February 1941.

An analysis of the results of surgical drainage upon "primary" subacute and chronic putrid lung abscess is presented. Subacute abscess is defined arbitrarily as one of seven to twelve weeks' duration. A chronic abscess is defined as one of more than twelve weeks' duration. Subacute and chronic abscess may be of either the "localized" or "diffuse" type. The localized type is characterized by a mono- or multilocular cavity with limited surrounding pulmonary infiltration. The diffuse type is characterized by multilocular or multiple cavities with more or less extensive surrounding pulmonary infiltration, induration, fibrosis and bronchiectasis. The great majority of primary (previously unoperated) cases of subacute abscess were of the localized variety. Approximately half of the chronic abscesses, whether primary or secondary, were of the localized type.

Operations in all cases consisted of drainage or attempts at drainage. Cure resulted after operation upon the localized form of subacute pulmonary abscess in all patients who survived. Operation on the diffuse form of subacute pulmonary abscess was fatal in all cases. The chief causes of mortality after operation for subacute abscess were pleural infection, which is avoidable, and spillover gangrenous bronchopneumonia, which is probably unavoidable.

The results of operation upon the localized form of chronic abscess, whether primary or secondary, were good. On the other hand, the results of operation upon the diffuse form of chronic abscess, whether primary or secondary, were bad, and the mortality was very high.

The differentiation between the localized and the diffuse form of subacute and chronic pulmonary abscess is based upon roentgenography and bronchoscopy, and bronchography in selected cases.

Subacute and chronic putrid pulmonary abscess complicated by putrid pleural infection presents special features and comprises a separate problem.

The Treatment of Spontaneous Breast Adenocarcinomas in Mice with Spleen or Yeast Extract. R. Lewisohn, C. Leuchtenberger, R. Leuchtenberger, and D. Laszlo. Am. J. Path. 17: 251, March 1941.

This paper presents further details of technical improvements in the methods of producing spleen and yeast extracts and a report of 38 out of 189 (20 per cent) spontaneous breast cancers in mice which regressed following intravenous injections of these extracts. The lowered rate of regression compared with the 30 per cent usually obtained in this treatment is explained by a severe intercurrent infection which killed many of the 189 mice with which the experiment was begun.

Autopsies of 5 healed animals, the tumors of which had been biopsied and diagnosed as malignant, and which died 149, 129, 93, 49, and 19 days, respectively, after they had been pronounced healed, revealed neither macroscopic nor microscopic evidence of cancer.

Roentgenoscopy as a Diagnostic Aid in Coronary Occlusion. A. M. Master. Am. J. Roentgenol. 45: 350, March 1941.

Roentgenoscopic (fluoroscopic) observations of ventricular contraction in 300 patients were reported. Half of these had had coronary occlusion; the remainder included other types of heart disease and also normal subjects used as controls.

Roentgenoscopy was shown to be a simple method of diagnosing a coronary occlusion with myocardial infarction. In coronary occlusion 75 per cent revealed abnormalities in pulsation. Systolic expansion, that is, reversal of pulsation, was observed in at least one-half of the patients and is considered characteristic of this disease. Absence and marked diminution of pulsation were present in the other 25 per cent of the cases and although definitely abnormal were not considered characteristic of the disease.

In the normal heart controls, the abnormal pulsations described were not present.

The Treatment of Carcinoma of the Ovary. R. I. Walter, A. L. Bachman, and W. Harris. Am. J. Roentgenol. 45: 3, March 1941.

The authors present a clinical and histologic study of 124 cases of carcinoma of the ovary and compare the results of surgical, x-ray, and combined therapy. The conclusions were: (a) The major factor in prognosis and determination of the type of therapy to be employed is the clinical stage of progression of the disease. Morphologic classification and histologic grading appear to be of minor importance. (b) Surgery plus adequate postoperative radiation yields a greater percentage of 5-year cures than surgery alone. (c) Maximal dosage of radiation therapy should be employed whenever possible. Small "palliative" amounts play a minor role in the treatment of ovarian carcinoma. In advanced cases (Stage IV) preoperative radiation is advocated. (d) The rationale for permitting a normal uterus to remain *in situ* and employing it as a radium carrier in order to increase the intrapelvic dose is discussed.

Ileojejunitis. B. B. Crohn and A. M. Yunich. Ann. Surg. 113: 371, March 1941.

Twenty-two cases were studied in which the pathological process characteristic of terminal ileitis was observed to extend from the ileo-cecal valve to the duodenum. The usual large skip-areas were present; at times the lesion covered many segments together, leaving free other segments. Fistulas in this type of disease are unusual, as are masses and obstructive phenomena. The treatment is entirely medical. Prognosis depends upon the severity of the pathologic process. The disease is capable of healing with scarring in a large percentage of cases.

Differentiation of Acute Coronary Insufficiency with Myocardial Infarction from Coronary Occlusion. A. M. Master, R. Gubner, S. Dack, and H. L. Jaffe. Arch. Int. Med. 67: 647, March 1941.

A clinical and electrocardiographic study was made of 48 cases of acute coronary insufficiency, i.e., recent myomalacia without acute coronary occlusion. The myomalacia following coronary insufficiency differs, as a rule, from that following coronary occlusion by its focal and disseminated character and its localization in the subendocardium and papillary muscles of the left ventricle.

Clinically, coronary insufficiency is usually associated with some factor which increases the work of the heart or diminishes the coronary flow, most often in a subject with antecedent cardiac enlargement and coronary sclerosis. The precipitating factors in the series studied included: heart failure; shock due to operation; pulmonary embolism; acute hemorrhage and infection; marked tachycardia or bradycardia; acute anemia; aortic valve disease, and hypertensive crises.

The electrocardiogram of acute coronary insufficiency with infarction is characterized by the presence of a depressed RS-T segment and flattening or inversion of the T wave in two or more leads. The occurrence of an elevated RS-T segment or a Q wave, particularly

in lead I, is rare. The electrocardiogram thus differs from that of acute coronary occlusion in which the latter changes are common. The presence of a depressed RS-T segment in acute coronary insufficiency is attributed to the subendocardial localization of the infarction.

Intercapillary Glomerulosclerosis (Kimmelstiel-Wilson) and the Nephrotic Syndrome in Diabetes Mellitus. S. Siegal and A. C. Allen. Am. J. Med. Sc. 201: 516, April 1941.

So-called intercapillary glomerulosclerosis, described by Kimmelsteil and Wilson, has been associated with a clinical complex consisting of diabetes, hypertension and the elements of the nephrotic syndrome. The lesion was studied from the points of view of its distribution in diabetics and non-diabetics and the correlation of the extent of the lesion with the severity of the clinical picture. The lesion was found to occur in 35 of 105 consecutive diabetics, in 1 of 100 consecutive hypertensives, and in none of 100 consecutive non-diabetic, non-hypertensive controls. It was found further that the lesion occurred in patients with simply the diabetic component of the syndrome and without hypertension or albuminuria. In general, however, a positive correlation existed between the extent of the lesions and the degree of development of the syndrome.

Hepatic Duct Visualization Following Oral Cholecystography. B. Copleman and M. L. Sussman. Radiology 36: 465–467, April 1941.

Four cases are reported in which after cholecystography and the ingestion of a suitable meal, the cystic, common, and hepatic ducts were outlined.

Visualization of the hepatic duct system above the junction of the cystic and common ducts is unusual, and is considered to be abnormal. It is probably the result of an imbalance in the reciprocal innervation mechanism so as to permit spasm of the sphincter of Oddi while the gall bladder is contracting. It is possible that the roentgen finding described may be considered confirmatory evidence of the diagnosis of biliary dyskinesia.

NEW ASPECTS OF PULMONARY TUBERCULOSIS AND THEIR RELATION TO TREATMENT*

EDGAR MAYER, M.D. AND ISRAEL RAPPAPORT, M.D.

The fact has been sufficiently emphasized that the character of the tuberculous infection changes with the shifts in the epidemiologic environment. It has also been proven that the prevalent form of the disease and its pathogenesis changes with the epidemiologic phase in the community. That pulmonary tuberculosis now has taken on new aspects has been the subject of much recent discussion. These features which made the disease in many ways different from what it was a generation ago, are yet generally mistaken for new discoveries. These are attributed entirely to our recent refinements in methods of investigation such as x-ray studies and bronchoscopy. However, the fact has been overlooked that they are also logically explained by the shifts in the epidemiology of the disease. We wish to point out the significance of these changes in the prevailing trend of pathogenesis and in the clinical features of pulmonary tuberculosis, particularly as they relate today to the therapeutic management of the disease. The changes which have occurred already and are currently taking place in the present progressive downgrade phase of the epidemiology of the disease will best be appreciated from Charts I and II. The most important of these changes may be summed up as follows: In the environment of a generation ago, contact with tuberculosis was constant. The original infection was severe, reinfection from without was rare, and if it occurred, it did so only in later life. In the present environment, contact with tuberculosis is inconstant, the majority of infections are much milder, they tend to heal promptly and completely, and recur again throughout life even within a few years. Exceptions are those remaining "nests" in certain areas and groups where tuberculosis is still near its epidemiologic peak; or where intensive exposure still exists, such as in tuberculosis institutions.

Recurrent exogenous infections. The prevailing epidemiologic conditions are characterized by: (a) vastly reduced contacts, both in number and intensity; (b) attenuated infections; and (c) evanescent allergy. As a result of these, recurrent tuberculous infections "primary-like" in character are common in our midst now. Both pathologic evidence and clinical roentgenological observations indicate a rising incidence of recurrent infections. An ever increasing proportion of first infections in children and adolescents and even adults is now so ephemeral that both the lesion and the allergy soon become extinct leaving the individual accessible to recurrences of exogenous infections. An "x-ray" lesion newly discovered in the lungs of an adult recently shown to have been tuberculin-negative now often represents a second so-called "primary" lesion. It is now not

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CHART I

Features of Three Epidemiologic Phases

	UPGRADE	PEAK	DOWNGRADE
Community	Virgin	Tuberculized fully	Detuberculization. Focalization
Mortality	Rising	Highest	Declining steadily
Morbidity	Rising	Highest	Declining steadily
Resistance	Low but rising	High	Beginning to decline
Allergy	Low but rising	High, prevalent and permanent	Declining incidence, evanescent character, resensitization
Contact	Increasing	Widespread and severe	Declining, particularly in severity and frequency
Infection	Rising incidence	Prevalent before adult age reached	Declining incidence particularly before adult age
Reinfection	None	None, hardly ever before middle age	Rising incidence throughout adult age
Disease	Acute and subacute generalized forms	Chronic endogenous phthisis and chronic hematogenous forms	Chronic exogenous phthisis
Latency	Infrequent, short	Prevalent and long between primary and chronic pulmonary tuberculosis between bouts of hematogenous dissemination	Declining and shortening between primary and chronic pulmonary tuberculosis

CHART II

Contrast in Chronic Pulmonary Tuberculosis

	AT THE PEAK	IN THE DOWNGRADE
Age prevalence	15 to 30	25 to 50
Recent exposure	Not important	Important
Allergy	Only tuberculin positives	Tuberculin negatives often predisposed
Source lesion	Mostly from lymphohematogenous secondaries	From recurrent "primaries" and secondaries equally often
Origin	Old endogenous	Fresh exogenous
Morphology at onset	Chiefly nodular	Often infiltration
Site	Mostly apical or subapical	Any lung area, four lobar apices frequent
Latency period of coalescence	Mostly long (10 years or more)	Often short (1 to 2 years)

uncommon to observe that such exogenous infections run the same course regardless of whether they represent the first, second or even any successive tuber-

culous reinfection of the same body from without. They may all be aborted in their initial, or in the "post-primary" lymphohematogenous phase. Any one of these infections, however, if severe enough occurring under conditions of exposure of the old type in close contact with open cases in homes or hospitals or if occurring when resistance happens to be low, may go on to progressive disease at any age. The peak of pulmonary tuberculosis is now toward middle age (35 to 45 years). In recent years it has become possible to follow cases in which after loss of sensitivity from the previous infection, a fresh infection produced lesions which have the appearance of either so-called "primary" or of the "reinfection type."

The evolution of recurrent "primary-like" lesions is in general the same as that of true "primaries." The bacilli after they have gained a foothold at some site in the lungs, usually produce a Ranke complex consisting of a parenchymal focus at the site of invasion and a lymphnodular focus at the hilum. The tendency of the infection is always to continue to invade the body from these primary sites by the lymphohematogenous route. The extent of this depends naturally on individual resistance. The route of invasion includes the combined lymph and blood channels from the thoracic lymphatics by way of the venous angle, the right heart and pulmonary circulation to the pulmonary capillary bed where the screening process again brings the bacilli back to the hilar lymph nodes by way of the pulmonary lymphatics. The more resistant the body and the more efficient this pulmonary screening, the fewer the bacilli that will get by the pulmonary circuit into the systemic circulation. The infection will then remain localized in the lymphohematogenous flow of the lungs. The lungs will then bear the brunt of the infection in the form of a post-primary lymphohematogenous dissemination.

The tubercle bacillus is a slowly multiplying organism; its first phases of penetration in the body are characterized by insidious latency. Particularly in long exposed communities where tuberculosis has passed its epidemiologic peak, the majority of the infected meet the invasion with sufficient resistance to make the infection either an altogether ephemeral one or at most an insidiously progressive latent process. The history of recent exposure or a recently acquired tuberculin sensitiveness in association with x-ray findings suggesting tuberculous lesions are now our chief diagnostic criteria for such an infection in its early phase.

The occurrence of an infection or reinfection may be evinced either by the lesions of the primary complex or by the lesions of the lymphohematogenous dissemination. In many instances the focus at the site of invasion is more conspicuous. In some instances the hilar pole of the primary complex is more conspicuous. In a considerable proportion of cases the lesions of the primary complex though inconspicuous were yet followed by a lymphohematogenous dissemination which soon becomes conspicuous by the progressive coalescence of these deposits in the apices of the four lobes, i.e., the upper parts of both lungs. Thus, the apical and subapical parenchymal lesions on both sides appear frequently as the first and only demonstrable lesions of an exogenous infection

when as a matter of fact they were but recently preceded by primary and lymphohematogenous phases which were not only clinically latent but also so undefined as to be hardly demonstrable even by x-ray examination.* The great difficulty of recognizing such a lymphohematogenous dissemination following a fresh infection was demonstrated with the force of a biopsy in a particularly instructive case reported by Brahdy. Often the latent phase manifests itself early by a simple pleural effusion when the termination of this phase and the apical coalescence of the lymphohematogenous deposits may still be months or even years away.

In the present era of serial x-ray survey of many adult contacts, the evidence indicates that chronic pulmonary tuberculosis develops more frequently than before in direct continuation of the "primary" lesion just described. This prompt progression is in part due to the somewhat greater tendency of these "adult primary-like lesions" to break down and spread locally from the site of exogenous invasion. This is particularly true where the second infection occurs in an environment of intensive contact (nurses, doctors, etc.). This greater breaking down tendency of recurrent "primary" lesions may be explained by the effect of abrupt resensitization following disappearance of a previous allergy.

A distinct tendency toward earlier confluence of the secondary lymphohematogenous deposits in the four apices has also been noted in these recurrent infections. Often no more than a few months up to one or two years elapse between the time of infection and progression to apical and subapical phthisical lesions giving the process the appearance of direct continuity. Less protracted evolution of the infection as a whole would explain this. As compared with the long telescoping-out of the process at the epidemiologic peak, we now have a beginning telescoping-in of the evolution of the process, in the present downward phase.

Any of these recurrent infections may result in chronic progressive pulmonary tuberculosis, which may develop from one of three possible sources:

a) From the focus at the site of exogenous invasion, by breakdown and local spread (chronic phthisis with infiltrative onset).
b) From the hilar lymphnodular focus by direct extension through a bronchial wall (bronchopulmonary tuberculosis).
c) From progressive apical and subapical secondary lesions of lymphohematogenous origin (chronic phthisis of nodular disseminated onset).

1. *Pulmonary phthisis* of infiltrative onset may range from minimal infiltrations and complete latency to large size pneumonic lesions and acute disease. They may become completely aborted, soon leaving a chalk-encrusted small residue. They may persist for a long period, may be round and large like a "tuberculoma," and eventually become calcified. They may break down and extend as bronchogenic phthisis either in slowly progressive nodular form or in subacute to acute infiltrative (bronchopneumonic) form. In their minimal la-

* In a recently tuberculin-negative young woman following a fresh infection, a lobectomy for leiomyoma showed in the excised lobe evidence of disseminated tuberculosis although it could not even be suspected by clinical or x-ray evidence.

tent phase these lesions can be detected only accidentally or by modern case finding methods of periodic x-ray examination of large numbers of exposed adults. No matter how early discovered or how closely observed, some of these recurrent infections give rise to infiltrations which show an early breaking down tendency and extend rapidly to involve entire lobes of a lung before the patient or the doctor has become aware of it. Recent experience indicates that lesions of the latter type are now more frequent under heavy exposure in tuberculin-negative young adults than was the case previously when young adults were long tuberculin-positive before such exposure.

2. *Bronchopulmonary phthisis* by direct extension from the hilar lymph node toward the bronchial wall and hence to the lung parenchyma, was not infrequent formerly in severe childhood primary complexes. We are under the impression from recent experience that this mode of extension of pulmonary tuberculosis is now more frequent in adults than was the case before. In the discovery of this new feature bronchoscopy was of decided assistance. It is quite probable that recurring exogenous infections account for a considerable part of the rising incidence of this type of extension in adults.

3. *Chronic bronchogenic phthisis* from progressive apical and subapical cortical deposits of the lymphohematogenous dissemination is still the most frequent form of chronic pulmonary tuberculosis. As explained above in most instances it originates with a group of nodular foci sprouting into the lung parenchyma in the upper thirds of one or both lungs (i.e., the apices of the four lobes). At times it appears in the form of a somewhat widespread progression throughout one or both upper lobes as if the interstitial tuberculosis had at once proceeded toward rapid sprouting into the alveoli, not unlike the sudden spring-like blossoming of trees. Naturally the more extensive and rapid this process, the earlier the nodules are likely to become confluent and will then tend to break down. Thus, at times a chronic lesion consisting of productive tuberculosis may show a greater breaking down tendency than will a large infiltrative lesion. The more frequent form of apical and subapical tuberculosis is the slow apico-caudal spreading nodular lesion.

Combinations of the three forms. The recent tendency towards more rapid evolution of the infection has brought about an overlapping between the phases resulting in combinations of two or even all three of the above forms with the following implications:

A primary-like tuberculous infiltration in any part of the lungs in its direct progressive course may become complicated sooner or later by involvement of the stem bronchus by direct extension from the lymphnodular focus in the hilum. Eventually progressive foci may make their appearance from lymphohematogenous secondaries in the apices of the lobes and extend downward at first by contiguity. Recent observations suggest to us that often a breakdown of the "primary" focus, particularly if it happens to be in the apex of one of the lobes, is precipitated by the development and succeeding coalescence of the lymphohematogenous deposits in the same area. In their subsequent course these bronchogenically spreading processes will soon coalesce and become continuous

beyond possibility of separation and recognition. Unless the opportunity is afforded as is now often the case to observe the evolution of these sequences from an earlier phase, the process will soon present a hopeless riddle as far as pathogenesis is concerned.

NEW TRENDS IN THE TREATMENT OF TUBERCULOSIS

The changes discussed above have materially affected the principles which underlie our methods of treatment, namely:

1. *Constitutional therapy* is still the only treatment we know of for reestablishment of resistance to tuberculosis in the body.

2. *Collapse therapy* is still our only means to overcome mechanical obstruction to healing created by tissue defects of an extent not likely to become obliterated spontaneously.

In short, the early systemic phases of the tuberculous infection call for constitutional therapy, while the treatment for bronchogenic spread is collapse therapy. As was mentioned above, the increasing shortening of the latency period between infection and progressive pulmonary tuberculosis has brought about much overlapping between the early systemic phase of tuberculosis and the succeeding phthisical phase. This calls for the application of a combination of prolonged constitutional and collapse therapy on an increasing scale in many instances where before the therapeutic problem was chiefly one of mechanical control of bronchogenic spread. The judicious application of combined constitutional and collapse therapy and their administration in a manner indicated by the particular requirements of the case, must be based upon our interpretation of the character of the pulmonary lesion in question. In order to treat properly, every attempt must be made to reconstruct the evolution of the individual process, in short, to answer the following two questions: What phase of the tuberculous process do the lesions represent? What is the potentiality of these lesions for progression? The answer to either one of these questions often applies to the other. It will be well to recapitulate here the potentialities of the main types of lesions discussed above.

In the first place, ability to progress promptly to chronic phthisis is possessed by the extensive infiltrative lesion at the site of invasion. The lymphonodular hilar lesion showing extension to the bronchial wall is also characterized by the same double potentialities of systemic and phthisical extension. Apical and subapical nodular deposits mostly bilateral are characterized by their conspicuous phthisical potentiality. While their rate of progress is much slower, their tendency to ultimate phthisical evolution is, judging by incidence alone, perhaps foremost. This is particularly so if and when they begin to show signs of confluence. Combination lesions indicate a rate of progress which speaks for itself. These potentialities are clear guides to the therapeutic indications.

The present era of x-ray surveys has created new therapeutic problems, namely that of the treatment of the latent minimal early "infiltrate," the so-called primary type lesion. In this initial phase these lesions show great tendency toward healing and if treated with bed rest, do so by resolution or

calcification in the vast majority of cases. The same may also be said even of the very transient and discrete lymphohematogenous dissemination which goes with such mild infections. Difference of opinion exists as to what proportion of these lesions would heal without rest. Most observers believe only a minority do so, while the majority progress. A few believe the opposite.

Can this difference of opinion be due to the fact that it is often not possible to distinguish between such latent "primary type" lesions in their natural course of healing and the superimposed lesions which result from confluence of secondary lymphohematogenous deposits particularly when both happen to be in the apical and subapical areas? The problem becomes involved by the fact that in a certain proportion of cases, even after the first lesion has undergone healing by resolution or by calcium incrustation, progressive phthisical lesions may soon develop from lesions that were deposited by the lymphohematogenous system in the same subapical cortical area. It is for these reasons that it is now necessary to subject all patients in whom a lesion, no matter how minimal, is discovered for the first time, to a rest period of from three to six months, followed by a few years of observation. The duration of the rest period should be determined by the behavior of the lesion.

In the presence of a persistently and completely subclinical (latent "primary" type) lesion, we believe the period of rest should not exceed about six months. It seems to us unreasonable to subject these patients to years of rest for the treatment of such a lesion, particularly since the postprimary lymphohematogenous latent period may last for years. Even a rest treatment of two years will not eliminate, in some cases, the possibility of progression from a secondary lesion at the end of that period. It is more important to keep these patients under close constant observation than to keep them at rest all that time.

It seems to us that the institutionalization in tuberculosis hospitals of patients in whom minimal lesions have been detected in routine x-ray surveys lacks logic. This is particularly apparent when we see that young hospital attendants who have acquired such lesions in their occupations by interrupted contacts, are promptly put alongside of their tuberculous patients for continuous contact just as soon as x-ray evidence of a lesion has been detected. It is our opinion that constant exposure to open cases of tuberculosis in this critical and comparatively early phase of the tuberculous infection is harmful in some, if not in all, such cases. It is our belief, therefore, that in tuberculosis sanatoria or hospitals these patients should be separated from open cases.

The treatment of a tuberculous lesion at the site of invasion should be conservative as long as possible for more than one reason. In the first place the spontaneous healing tendency of these lesions under rest is quite remarkable. Large infiltrations may resolve just as rapidly as they have appeared, and even early thin walled cavities show a surprising tendency toward rapid closure on bed rest alone. Some do so earlier, some later. Another reason for conservative treatment is that the infection may still be in the phase of lymphohematogenous dissemination with its source in the lymphnodular focus. Chronic bronchogenic phthisis may, therefore, follow later from apical and subapical

secondary lesions, even long after arrest of the primary lesion. Collapse therapy for the local lesion should not be carried out until ample time has passed to observe the trend of evolution of infection in the body and after the tuberculous process in the lung has been treated constitutionally. Successful collapse therapy often fails dismally because of failure to gauge properly the phase of the tuberculous infection in the body as a whole.

Many clinicians believe apical and subapical productive tuberculosis is harmless. We believe this opinion to be wrong and based on observations of a large number of obsolete lesions in the apices of older patients or on observations of young adults a generation ago, who presumably had their first infections in childhood. In young individuals of today, apical and subapical productive tuberculosis is still a frequent point of issue for progressive tuberculosis of the lungs. The fact cannot be overemphasized that such nodular lesions often continue on their slow but relentless progression from small beginnings. These nodular lesions apparently respond temporarily to treatment but in the long run they tend to progress. Furthermore, they are often bilateral from the beginning or become so eventually. It is not generally realized how often the new lesions are due to lymphohematogenous dissemination where the source of bronchogenic spread was long sealed by effective pneumothorax. Unless we employ here constitutional treatment liberally to arrest the tuberculous process in the body at an early phase, our efforts at blocking progression mechanically by collapse therapy will be defeated in the long run.

Progressive bronchopulmonary tuberculosis by extension from the hilar lymphnodular focus through invasion of the bronchial wall is now often a very vexing clinical problem. Its treatment is beset with many new difficulties which are only now being worked out in the light of current experience. It is yet too early to even indicate the trend.

CONCLUSIONS

Under the prevailing epidemiologic conditions, recurrent tuberculous infections "primary-like" in character are becoming increasingly frequent in our midst.

Any of these recurrent infections may result in chronic progressive pulmonary tuberculosis which may develop in three forms: a) by breakdown and local spread from the site of invasion; b) by extension from hilar lymphnodes directly to the bronchial mucosa; c) by coalescence of apical and subapical cortical secondary foci of lymphohematogenous origin.

A combination of these modes of extension are frequent and obscure the individual pathogenesis of chronic bronchogenic phthisis.

In the present era of x-ray surveys of healthy contacts we find many infections in their early latent phases when it is not yet possible to distinguish between well controlled lesions in their natural course of spontaneous symptomless healing and lesions which already represent the latent incipient phases of phthisis and are liable to progress. Many of these infected individuals are subjected to perhaps superfluous prolonged periods of rest. In view of the dangerous po-

tentialities of a considerable proportion of these lesions, this measure seems justified but it should not be prolonged beyond reason.

In the present epidemiologic phase, bronchogenic extension from the site of invasion and postprimary lymphohematogenous dissemination frequently overlap in time as well as in space. Collapse therapy for the former and prolonged bed rest for the latter must now be continued more often in combination. In these "primary-like" infections, collapse measures alone, no matter how successful in controlling local extension, will not prevent progression of the lymphohematogenous dissemination. Contralateral lesions of lymphohematogenous origin are often the cause of failure of collapse therapy. Permanent collapse measures should be delayed until the trend of the infection in the body as a whole has been observed.

RADIATION CANCER

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A recent case of radiation sarcoma of the skin, reported by Dr. E. E. Arnheim in this issue of the JOURNAL OF THE MOUNT SINAI HOSPITAL, stimulated an interest in the subject of neoplasms produced by radiation. Many articles have already been written on this subject but mainly on the surgical aspects of treatment. The purpose of this article is to review in a concise manner the different types of radiation tumors that have been described and the essential facts concerned in their production.

Radiation cancer is a term which may be applied to any type of cancer in which irradiation plays an etiologic rôle. The form of the radiation may be x-rays or any radioactive element. The radioactive elements chiefly concerned are radium, radon, and thorium.

In the early years of radiology when the methods of measurement of radiation were inaccurate and when the effects of irradiation were not too well understood, radiation injuries were common. These injuries not only resulted in serious irreparable damage to tissues but often predisposed to the formation of cancer in the damaged tissues.

Three groups of individuals were subject to radiation cancer: 1) Those who worked with x-rays and radioactive elements; 2) patients on whom x-rays or radium were used for diagnostic or therapeutic purposes; and 3) industrial workers who came in contact with radioactive elements.

The first group, those who worked with x-rays and radioactive elements, includes all the pioneers in x-ray and radium research as well as physicists, manufacturers of x-ray tubes, technicians, especially those working in radon plants, physicians, and dentists. The largest number of sufferers came from this group. The most common site of radiation cancer in this group was the hand, especially on the dorsal surface. This was probably related to the fact that the hand received the greatest amount of exposure during such practices as fluoroscopic examinations, the holding of a cassette in the taking of a portable roentgenogram, or the preparation and handling of radium applicators. Other parts of the body, however, were equally as vulnerable if exposed. Lesions on the face were also frequently reported. Another important etiologic factor was that the exposure to radiation was usually prolonged over many years. While a single exposure by itself was of only slight effect, the frequently repeated exposures were cumulative in their action on the tissues. The prevention of injuries in this group can be effected by strict adherence to the rules of protection established by the National Bureau of Standards.

The second group of sufferers comprised patients on whom x-rays or radium were employed for either diagnostic or therapeutic purposes. Many injuries were inflicted by prolonged and repeated fluoroscopic examinations, or by the

prolonged exposure necessary for a roentgenogram. Overtreatment, particularly for a benign condition, such as hypertrichosis, lupus, or eczema, was another frequent cause of radiation injury and subsequent cancer formation. Permanent epilation by radiation methods was a common practice in beauty parlors many years ago, with the result that today there are numerous cases of carcinoma arising in these damaged areas of skin. In lupus, carcinoma may arise spontaneously, but the incidence of development of carcinoma in lupus was greatly increased by prolonged, repeated radiation therapy. Another method of radiation injury to patients was the ingestion or injection of radioactive substances. As in the first group, an important factor in the etiology of radiation cancer was that the exposure to radiation was repeated and prolonged over many months or years.

The third group comprises workers in two special fields of industry: the luminous watch dial painters and the miners in the Schneeberg and Joachimstal mines. The dial painters in the luminous dial factories of New Jersey, New York, and Connecticut ingested radium in the course of their occupation, daily small amounts over a period of several years. As a result there occurred numerous fatalities in the form of osteo-radio-necrosis of the jaws, a peculiar form of aplastic anemia, and osteogenic sarcoma. In the Schneeberg and Joachimstal mines, the miners suffered from a very high incidence of carcinoma of the lungs. This was associated with the inhalation of radon, a radioactive gas, which was present in the atmosphere of these mines in appreciable amounts. The bone sarcoma of the dial painters and the pulmonary neoplasms of the Schneeberg and Joachimstal miners may both be classified as occupational cancers.

The various types of radiation cancer observed in man may be grouped as follows:

1. Radiation Cancer of Skin
   a. Squamous cell carcinoma
   b. Basal cell carcinoma
   c. Spindle cell sarcoma or spindle cell variant of epidermoid carcinoma
2. Radiation Cancer of Bone
   a. Osteogenic sarcoma
   b. Fibrosarcoma
3. Radiation Cancer of Lung and Pleura
   a. Epidermoid carcinoma
   b. Small cell carcinoma
   c. Oat cell carcinoma
   d. Polymorphous cell carcinoma
4. Radiation Cancer of Liver
   a. Malignant hemangio-endothelioma
5. Radiation Leukemia
   a. Lymphatic type
   b. Myelogeneous type

It is of special interest to note that there are no recorded instances of radiation cancer of the gastro-intestinal tract or urinary bladder in man, although reports of radiation injuries to these organs are numerous.

Radiation Cancer of Skin: Radiation cancer of the skin follows a definite sequence of events. It occurs only in skin that has undergone certain well recognized changes resulting from irradiation. The gross appearance of this "roentgen skin," as it is sometimes called, is characterized by atrophy, telangiectasia, mottled pigmentation, and loss of elasticity. The altered area of skin may be depressed below the level of the surrounding normal skin. There is loss of hair and loss of sebaceous and sweat gland secretion. The texture is coarse, leathery, and thickened. Keloid formation, however, is practically unknown in this type of skin. Keratoses and ulcerations are common. Resistance to infection is poor and healing is slow and delayed. Occasionally, roentgen skin may break down and develop into a chronic indolent ulcer which heals with difficulty. Cancer may arise at the edge of such an ulcer.

Microscopically there is complete loss of all appendages such as hair, sebaceous glands, and sweat glands. There is increased density of the subcutaneous connective tissue in which the normal collagen is replaced by a dense hyaline collagen rich in elastic fibers but poor in cells. Obliterative processes are present in all the vessels. There is compression of lymphatics and capillaries by the diffuse hyaline fibrosis except in the papillae of the corium where the capillaries are dilated to form telangiectases. These are frequently thrombosed and surrounded by small zones of necrosis. The larger vessels are obliterated by proliferation of the endothelium and by marked thickening and hyalinization of the media. The epidermis presents a varied picture which indicates that it is in a much more active state than normal. Numerous local areas of epithelial hypertrophy correspond to the keratoses seen grossly. In other areas, the epidermis grows deeply below superficial zones of necrosis beneath the corium. It is in these areas of epithelial downgrowths and keratoses that carcinoma may arise.

Three types of malignant neoplasm arise in roentgen skin. The commonest type is squamous cell carcinoma which behaves like the spontaneously occurring variety. Its rate of growth may be slow or fast, it is infiltrating in character, and it metastasizes to the regional lymph nodes. Distant metastases to liver, lungs, and other viscera occur in late stages of the disease. The primary lesions are frequently multiple. The second type is basal cell carcinoma which is very much less common than the squamous cell variety. The third type is spindle cell sarcoma. While this type is of relatively rare occurrence in man, it is quite easily produced experimentally in animals. In man, it may occur more frequently as a sequel to prolonged irradiation of lupus lesions. It may also simulate a recurrence at the site of an epidermoid carcinoma previously treated by irradiation. Its course is more rapidly malignant than that of squamous cell carcinoma. It infiltrates more widely and more deeply and also metastasizes to regional lymph nodes. Local recurrences are frequent after surgical excision. There is not complete agreement among pathologists as to the true sarcomatous nature of these lesions. While many pathologists definitely regard them as sarcomas, others believe they are carcinomas. A few pathologists described them as an atypical form of reparative process or granulation tissue. Stewart and Martin, in a review of this subject believe that these tumors are spindle

cell variants of epidermoid carcinoma even though the microscopic appearance is that of spindle cell sarcoma.

The changes characteristic of roentgen skin usually appear one or two years or more after irradiation. Radiation cancer, however, appears much later. The time interval from the onset of irradiation to the appearance of a malignant neoplasm may vary from one to twenty-five years. The average interval is about eight or nine years. The first case of radiation cancer of the skin was reported in 1902 by Frieben, in an x-ray tube maker, six years after the discovery of x-rays. Numerous case reports soon followed. The incidence is now low, but, in the early years of radiology, it must have been very high. There are no statistical studies to confirm this impression. The mortality has been estimated by various authors at about 25 per cent. Age is not a factor. The essential factor is a peculiar type of injury to skin and subcutaneous tissues in which repair is never complete but characterized by active processes and degenerative processes constantly occurring together. Wolbach, who made detailed studies of these processes, believed that the fundamental changes are in the blood vessels. The gradual obliteration of the blood vessels results in a form of progressive aseptic necrosis of the connective tissue, whereas the epidermis, in response to this form of necrosis, actually becomes more active than normal. The increased activity of the epidermis is evidenced by the development of keratoses and epithelial downgrowths. These manifestations precede the appearance of a neoplasm and it is this reparative activity of the epidermis that finally assumes a neoplastic character. The whole process is slow and requires many years before malignant change becomes manifest. In this respect, this train of events is analogous to the processes occurring in leukoplakia, lupus, senile skin, sailor's skin, farmer's skin, and xeroderma pigmentosa—in all of which, malignant neoplasm is a common complication.

The amount of radiation necessary to initiate the entire train of events is not known. In the great majority of instances, the radiation was administered repeatedly in small doses, over a long period of time. Those who worked with x-ray or radium were repeatedly exposed to small doses of radiation over a period of many years, thus leading to an accumulation of tissue damage which soon became irreparable. The typical history, in patients, was that a series of treatments was repeated frequently over a course of months or years, often for some condition which in itself was of a chronic nature.

Roentgen skin is not to be confused with the acute radiation reaction consisting of erythema, vesiculation, and pigmentation which appears at the end of a well planned course of irradiation, and from which there is usually complete recovery. Roentgen skin may appear long after the skin has completely recovered from the acute reaction, or, very often, without there ever having been an acute reaction.

The treatment of radiation cancer of the skin is complicated by the presence of tissue which heals poorly. Most surgeons are agreed that the entire area of roentgen skin in which cancer has developed should be excised and that the incision should also be deep enough to reach normal healthy tissues. This often

requires extensive plastic procedures. Sampson Handley further recommends regional lymph node dissections in all cases, not omitting the epitrochlear node in the case of carcinoma of the hands. For small lesions such as keratoses and fissures, the various recommended methods are excision with skin grafting, fulguration, actual cautery, carbon dioxide snow, caustic chemical agents, radium, and "short distance" x-ray therapy. Each method, if properly employed, is useful in individual cases. However, as Porter stressed many years ago, the most conservative procedure is really radical surgery because of the progressive nature of this disease. With any other method, there is always the danger of failure to eradicate the lesion, poor wound healing, recurrences, or the development of new lesions in tissue already so predisposed.

Radiation Cancer of Bone: While the majority of skin injuries were due to x-ray and relatively few to radium, all of the bone lesions reported were due to radium. Martland reported nine cases of osteogenic sarcoma in radium dial painters, eight from a New Jersey factory and one from a worker employed in both New York and Connecticut factories. The victims were all girls. The paint consisted of crystalline zinc sulphide mixed with small amounts of radium, mesothorium and radiothorium. Owing to a habit of pointing the paint brushes with their lips, these girls swallowed small amounts of the radioactive paint daily. In this manner, an appreciable amount of radium and thorium was ingested, absorbed, and eventually deposited in all the bones of the skeleton. Within an individual bone, the distribution was irregular, with larger amounts present in the dense outer cortex. The time of employment varied from one to four years. The time of appearance of osteogenic sarcoma varied from four to fourteen years from the beginning of employment or about eight or nine years after these victims had stopped working as dial painters.

During this long latent period, although the girls appeared outwardly in good health, the action of the radium on the bones and bone marrow was constant and unremitting. In every case there developed, at first, diffuse rarefying osteitis, "radiation osteitis," with red regenerative, hyperplastic or megaloblastic bone marrow. The latter was often associated with a leukopenic and agranulocytic blood picture. As a further stage, there occurred, in patchy areas over the skeleton, a very cellular replacement fibrosis of an intense inflammatory character, with mitotic figures and hyperchromatism, so that these areas could be distinguished from sarcoma only with difficulty. It was in these areas that sarcoma developed. Martland called attention to the similarity of the bone changes with the development of sarcoma in Paget's osteitis deformans and von Recklinghausen's osteitis fibrosa cystica.

All of the malignant bone lesions reported by Martland were osteogenic sarcomas, some of which were associated with fractures and bone deformities. The locations of the primary lesions were in the femur, scapula, pelvis, rib and orbit. In one case, there were two primary lesions; one in the orbit, the other in the pelvis. Metastases, when they occurred, were widespread. Histologically, many of the primary lesions were anaplastic. At the time of the report, six of the nine cases had died. The age of the victims varied from twenty to thirty-four years. The essential factor in these cases, as with the skin neoplasms, was

a type of injury to bone which, although irreparable, stimulated a prolonged reparative response that eventually became neoplastic in character.

A case of fibrosarcoma of the tibia was reported by Nørgaard in a woman who had received intra-articular injections of radium chloride in the right knee nine years previously for arthritis. The amputated specimen showed a fibrosarcoma of the tibia with radiation osteitis and hyperplasia of the bone marrow. The sequence of events was evidently very much the same as in Martland's cases of osteogenic sarcoma.

The estimated amount of radium absorbed in the entire skeleton of each of these cases varied from 10 to 180 micrograms. Practically all of it was in the bones. Ten micrograms of radium, although a minute quantity, ejects 370,000 alpha particles per second, so that over a number of years the number of ejected alpha particles is, literally, enormous. The alpha particle is intensely ionizing. Furthermore, the activity of radium is practically constant. The radium is permanently fixed in the bones where it probably replaces calcium, and is not excreted. This is analogous to the fixation of lead in bones in chronic lead poisoning. Therefore, ten micrograms of radium, when measured in terms of atomic activity over a period of years, is a tremendous dose. Although radioactivity was detected in all the bones of the skeleton and in the primary tumor, it could not be demonstrated in the visceral metastases.

Little can be said about the treatment of radiation osteogenic sarcoma. Unfortunately, the prognosis must be considered hopeless.

Radiation Cancer of Lung and Pleura: Since the year 1500, it was known that a large number of miners in the Schneeberg district in Saxony died from a pulmonary disease which only in recent years was found to be carcinoma of the lung. The high incidence of carcinoma of the lung among these miners contrasted sharply with its low incidence among people living in the same district but not working in the mines. Similar findings were discovered in the neighboring mines of Joachimstal in Bohemia.

In an investigation carried out in Schneeberg in 1922, it was found that 71 per cent of the deaths among miners were caused by carcinoma of the lung. In a more detailed investigation carried out in Joachimstal in 1926, it was found that carcinoma of the lung occurred chiefly in those miners who had been pensioned off for many years. The time of employment varied from thirteen to twenty-three years. Except for two cases, carcinoma of the lung did not appear until one to twenty-seven years after the miners ceased to work in the mines. The actual duration of symptoms varied from ten months to nine years. Post-mortem studies revealed that the primary lesions may arise anywhere in the lung,—bronchus, parenchyma, and, in one case, pleura. Widespread metastases were common. In another case, two separate and distinct primary lesions with different histology were found. The histologic picture was also varied—epidermoid, small cell, oat cell, and polymorphous cell carcinomas. While in the Schneeberg cases anthracosis and silicosis were common, these findings were rare in the Joachimstal cases. No associated pathologic conditions were found which might indicate a pre-cancerous stage.

In both the Schneeberg and Joachimstal mines, the air contains an appreciable

quantity of radon. Joachimstal acquired fame as one of the first discovered sources of radium. It was estimated that in the course of fifteen years, a miner may inhale the equivalent of fifty-five milligrams of radium chloride. Radon is an insoluble gas which is chemically inert. Consequently, it exerts its radioactivity upon pulmonary tissue only during its transient passage through the bronchi and pulmonary alveoli in the processes of respiration. It is not stored in the lungs or in any other part of the miner's body and no measurable quantities were found on autopsy. Although the evidence is by no means conclusive, it is the opinion of the investigators that the constant inhalation of the highly radioactive radon over a period of many years is the responsible etiologic factor.

Radiation Cancer of the Liver: An unusual case was reported by Ross of a woman in whom a radium needle was lost in the pericardium during treatment with radium needles for carcinoma of the breast. Death occurred three years later. At post-mortem examination, the needle was found embedded in heart muscle and surrounded by extensive hyaline fibrosis. However, six inches from the needle, in the left lobe of the liver, there was a large malignant hemangioendothelioma which had metastasized to the lungs. In view of the extreme rarity of this type of tumor, it is reasonable to exclude the possibility of coincidence and to assume that the constant radiation from the needle was responsible for its production. From the data given in the original article, it can be calculated that the region of the tumor received approximately 2000 gamma roentgens in the three years. This is about one-third the cancericidal dose of radium which is usually given within a period of one to three weeks. Thus, this case also illustrates the importance of the time factor.

Radiation Leukemias: An occasional case of leukemia, either lymphatic or myelogeneous in type, has been reported in x-ray and radium workers. For example, Haagensen reported a case of lymphatic leukemia in a nurse who took charge of radium applicators of various kinds for many years in a hospital where large amounts of radium were used. Because of the small number of cases reported contrasted with the large number of workers in the field of radiology who showed some form of change in their blood picture, most investigators regard as inconclusive the evidence for the production of leukemia by irradiation. The post-mortem examination of the case reported by Haagensen showed findings typical of lymphatic leukemia but without any other changes that might indicate a pre-neoplastic stage. It is probable that the incidence of leukemia in x-ray and radium workers is about the same as in the general population.

Experimental Radiation Cancer: With experimental animals, a great variety of tumors has been produced by irradiation. By implantation of radioactive elements in various tissues, tumors can be produced at the site of implantation. Usually many months are required before the tumor appears. In bone, osteogenic sarcoma, fibrosarcoma, and Ewing's tumor have been produced in this manner; in soft tissues, spindle cell sarcoma and myxosarcoma; in skin, squamous cell carcinoma. It is of human importance to note that with thorotrast (20 per cent colloidal thorium dioxide), spindle cell sarcoma arose in the normal tissues surrounding thorotrast granulomas. There are no case reports of the

cancerogenic action of thorotrast in man, but in the light of these animal experiments, the use of thorotrast in man should be condemned.

Ovarian tumors such as tubular adenomata, granulosa cell tumors, and lutcomata have been produced in mice by x-rays.

The cancerogenic properties of ultraviolet radiation may be mentioned at this point. Ultraviolet rays penetrate the epidermis and cause superficial skin changes similar to those produced by x-rays. Numerous experiments with mice exposed to ultraviolet radiation or sunlight over a prolonged period of time reveal that tumors may arise in those parts of the skin not protected by hair and therefore directly exposed to the radiation. Tumors were found on the ears, eyelids, tails, and dorsum of the forepaws. The histologic types of skin tumors produced were squamous cell carcinoma and spindle cell sarcoma in about equal proportions, often multiple with both types occurring in the same animal. As with the radiation spindle cell sarcoma in man, the same dispute exists as to whether this spindle cell sarcoma in mice is a variant of epidermoid carcinoma or a true sarcoma. These experiments in mice are analogous to the observations in man of the destructive and cancerogenic properties of sunlight in "farmer's skin," "sailor's skin," and xeroderma pigmentosa.

Epithelial tumors may also be produced experimentally by irradiation of a pre-cancerous skin lesion with moderate doses that are insufficient to destroy the lesion. These experiments are in accord with the observations in man that a combination of cancerogenic agents may be more effective in producing cancer than any single agent. For this reason, Mottram cautions against the treatment of such pre-cancerous conditions as leukoplakia or Schimmelbusch's disease with insufficient doses of radiation.

CONCLUSIONS

The various types of radiation cancer, both human and experimental, have certain fundamental features in common. The exact amount or dose of radiation necessary for the production of radiation cancer is not known, nor is it so important as the fact that the radiation must be administered over a long period of time—the time factor. Seldom does a single exposure initiate the train of events that leads to cancer formation. A long period of exposure is required, varying from a few months to several years. The exposure may be either continuous or intermittent.

Radiation is essentially a destructive agent. If given in doses sufficient to destroy tissue completely, beyond any chance of repair, a condition known as radionecrosis is produced. Radionecrotic tissue, being practically devoid of any viable elements seldom undergoes malignant change but cancer may occur in the viable tissue at the edge of a radionecrotic area. However, if the dose of radiation is such as to produce incomplete destruction or differential destructive effects on various tissue components, then a complex balance of necrosis and repair is set up which may eventually lead to malignant neoplasm formation. The injury so produced in the irradiated tissues is of such a character that both degenerative and regenerative processes occur side by side at the same time.

Both processes are progressive and continue indefinitely even though the injurious agent may be withdrawn. This is the stage which corresponds to the long latent period between the administration of radiation and the appearance of neoplasm. This period is extremely variable and unpredictable in length. It may vary from one to twenty-five years. However, all during this period both reparative and degenerative processes are active, but neither repair nor necrosis is ever complete.

Finally a stage is reached in which the reparative processes undergo such increased activity that a transition to neoplastic activity occurs. Because of the peculiar nature of this pathological process, neoplasms arising in this type of tissue are frequently multiple. In the skin where these events are best observed, every stage of transition may be found from simple hyperplasia of the epithelium to infiltrating squamous cell carcinoma, but in a stroma characterized by extensive hyalinization and poor vascularity. The histological type of neoplasm is dependent, not upon the nature of the injurious agent, but upon the type of tissue affected by the radiation. The neoplasm is limited in origin to the irradiated tissue, but once established, it behaves like any other malignant neoplasm of similar histology and similar anatomic site of origin.

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SARCOMA OF THE NECK FOLLOWING ROENTGEN THERAPY IN GRAVES' DISEASE

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The development of malignant neoplasms of the skin following roentgen radiation has been recognized for many years. A detailed discussion of the subject has been presented by Silverstone (5). The most common type of radiation malignancy is squamous-cell carcinoma. Sarcoma following roentgen radiation is rare. The following is the first reported case of sarcoma of the neck following roentgen therapy of Graves' disease.

CASE REPORT

History (Adm. 198899). P. D., a woman, aged 28 years, was first admitted to The Mount Sinai Hospital on February 14, 1920, with the complaints of nervousness, weakness, palpitation, dyspnea on exertion, sweats, loss of weight, and swelling of the neck, all of six months' duration. The symptoms were first noted about one month after a fire in the patient's home.

Examination. The abnormal findings were as follows: enlargement of the thyroid gland, over which a bruit was heard and thrill was felt; exophthalmos; tremor of the hands; tachycardia (pulse rate 136). The basal metabolic rate was plus 42 per cent.

Course. The patient was hospitalized for a period of three months. The treatment consisted essentially in rest in bed and roentgen radiation of the thyroid gland. The number of treatments and the x-ray dosage are not known. On discharge from the hospital on May 6, 1920, the patient had gained 24 pounds in weight, and the pulse rate was 90. After discharge from the hospital roentgen therapy was continued, but again the number of treatments and dosage are not known.

Second Admission (Adm. 450797). The patient was readmitted to the hospital on January 5, 1940, twenty years after the first admission. She noted some reddish brown spots in the front of the neck two years after the previous discharge from the hospital This area of discoloration gradually spread over a period of years. Eight months before admission a painless swelling, about the size of a pea, was found in the lower part of the right side of the neck. This lump gradually increased in size.

Examination. There was a mass about three centimeters in diameter in the right side of the neck just above the clavicle over the sternomastoid muscle. The mass was firm, smooth in outline, and fixed to the skin but not to the underlying muscle. The skin around the mass was pigmented and showed many areas of telangiectasis; the skin over the anterior chest wall in the upper sternal region showed similar changes. There were no clinical manifestations of Graves' disease and the thyroid gland was not enlarged.

Operation. Gas, oxygen, and ether anesthesia was administered, and the tumor together with a segment of overlying skin was excised through elliptical transverse incisions. The tumor was firm in consistency, yellowish-white in color, and lay in the subcutaneous tissues superficial to the cervical fascia and adherent to the skin. The histologic report of the tumor was "fibrosarcoma showing infiltration of fat tissue and muscle."

In view of this report, the neck was again explored ten days later. No gross tumor tissue was found, but a section of the sternomastoid muscle and fascia at the base of the wound was excised. A further excision of the skin at the edges of the wound was also performed. The histological report was "a small area of fibrosarcoma in the subcutaneous tissue attached to one of the skin specimens; the muscle and fibrous tissue show areas of acute inflammation" (fig. 1A). The wound was not sutured and healed by granulation.

Third Admission (Adm. 458642). The patient was readmitted to the hospital on June 20, 1940, five months after the previous admission. At a follow-up examination shortly before admission, a hard mass was found in the right side of the neck extending upward from the scar of the previous operation.

Operation. Gas, oxygen, and ether anesthesia was administered, and a dissection of the right side of the neck was performed through a long incision which extended from the angle of the jaw to the clavicle, passing on either side of the mass. The tumor was firm in consistency, grayish-white in color, and measured about 4 x 2 cm. in diameter. The mass was embedded in the sternomastoid muscle and seemed to arise from the cervical fascia. Healthy muscle was divided above the upper limit of the tumor, and a complete excision of the tumor and muscle was performed. In the course of dissection, much of the sternomastoid muscle was removed. The carotid sheath was opened and the tumor dissected from the internal jugular vein. At the site of the previous operation there was some scar tissue but no gross tumor. The histologic report was "fibrosarcoma; muscle tissue attached to the tumor showing early infiltration" (fig. 1B).

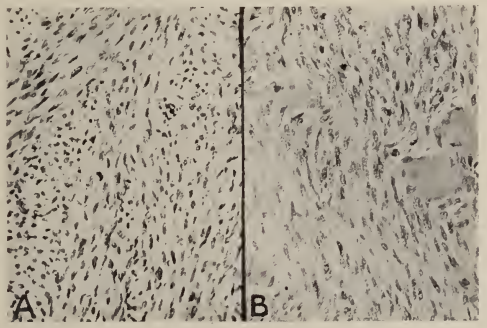

FIG. 1A. Section showing fibrosarcoma with some areas of acute inflammation (photomicrograph, ×375).

FIG. 1B. Section showing recurrent fibrosarcoma (photomicrograph, ×400).

Course. The postoperative course was uneventful. Most of the wound healed by primary union, and healing by granulation occurred in a small area of skin separation. The last follow-up examination was May 22, 1942, twenty-three months after the last operation. There was no evidence of recurrence of the tumor.

COMMENT

A study of the few case reports of roentgen sarcoma of the skin following excessive radiation, Bohmer (1), Deuticke (2), Kaplan (3), Witwer and Leucutia (6), reveal that these tumors have usually developed in skin areas treated for benign conditions: hypertrichosis, dermatoses and tuberculosis. The doses given for these conditions were small and repeated. Deuticke considered the relation of the roentgen radiation of lupus vulgaris to the development of sarcoma and concluded that roentgen radiation as such rarely resulted in sarcoma, but a coincidence of these two factors, tuberculosis and roentgen radiation, seemed to favor the development of sarcoma.

Prior to the manifestations of radiation malignancy, one or more of the degenerative radiation changes in the skin are evident: atrophy, telangiectases, pigmentation, ulceration. There is usually a long period of time, often many years, between the roentgen therapy and the appearance of the malignancy. Thus, with an overdose of roentgen radiation, permanent skin changes are produced and malignant degeneration may occur at any time later.

The roentgen sarcoma are of the spindle-cell variety. Martin and Stewart (4) reported four cases of this group which they considered spindle cell epidermoid carcinomas. In general, roentgen sarcoma is refractory to radiation, and complete surgical excision is the treatment of choice; local recurrences are common.

SUMMARY

The first reported case of sarcoma of the neck following roentgen therapy of Graves' disease is described. Degenerative radiation changes (pigmentation and telangiectasis) in the skin of the neck occurred two years after roentgen therapy for Graves' disease. Eighteen years later a fibrosarcoma developed at the site of these skin changes. Five months after excision of the tumor a recurrence was noted. A radical neck dissection resulted in freedom from recurrence for a period of twenty-three months.

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AN UNUSUAL EPITHELIOMA OF THE LEG

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Longevity and cancer are unwilling but constant bed-fellows. The progressive strides in medical science which have prolonged the average life expectancy have as a result increased the incidence of cancer in the mortality statistics. Macklin (1) paints a picture of mankind walking over the bridge of life which spans the river of death. On the bridge there are many trap doors—typhoid fever, small-pox, malaria—through which the unwary traveler may drop, but these seldom open now. So large numbers arrive at the end of the bridge and fall through a small number of wide doors, such as apoplexy, coronary occlusion and, above all, cancer.

In step with this march of anaplasia, there has been a corresponding increase in the incidence of cutaneous new growths. That these malignancies are not of the usual basal cell or squamous cell variety and do not always appear on the exposed body surfaces is a cogent point, generally unrecognized. These uncommon tumors are an important group, in view of their relatively high grade of malignancy. The purpose of this paper is to present one of these unusual cutaneous neoplasms and to discuss the complexities of differential diagnosis and therapy.

CASE REPORT

History (Adm. 449571). B. A., a 62 year old, white, foreign-born housewife, was admitted to The Mount Sinai Hospital on December 5, 1939, with a history of progressive growth and ulceration of several masses on her left leg.

There was no familial history of cancer. Her past history included typhoid fever at the age of ten and pneumonia at the age of forty-seven years. The recent history was negative for weight loss, headaches, abnormal or bloody stools, hematuria, jaundice, or pains in the bones. She had had no nausea or vomiting, her appetite was good and her diet was balanced and adequate. There was no history of the ingestion of iodized salt or of any drugs and there had been no exposure to any toxic substance.

In March 1939 the patient first noticed a pea-sized, red "spot" on the left shin. This area enlarged peripherally but did not become elevated or painful until April 1939. At this time it "broke open" and increased slowly in size. At the same time, several new adjacent lesions appeared. These grew, ulcerated, and became painful. A Wassermann test performed at this time was negative. The ulcerated growths slowly but progressively enlarged in spite of local therapy with various salves and she was referred to The Mount Sinai Skin Clinic where hospitalization was recommended.

Examination. The patient was an extremely obese, middle-aged woman, afebrile, and in no distress. The eyes, ears, nose and throat presented no abnormalities. The lungs were clear. The heart was not enlarged. A soft systolic murmur was heard over the aortic area and was transmitted to the pulmonic area and down the right sternal border. The rhythm was regular. The blood pressure was 134 systolic and 84 diastolic, and there was slight peripheral arteriosclerosis. The abdomen was obese but no masses were palpable. The skin was essentially normal except for that of the left lower extremity.

Over the left shin there were two irregularly rounded, palm-sized ulcers, and one quarter-dollar-sized ulcer about 2 to 3 cm. in depth with deep-red, elevated, nodular, firm borders. The surfaces of the ulcers were covered with an adherent, greenish-black, foul-smelling

slough. Below these ulcers there was a walnut-sized globular mass with a purplish-red but non-ulcerated surface. There was no surrounding lymphangitis or cellulitis and no adenopathy, either of the popliteal or inguinal nodes (figs. 1 and 2).

Laboratory Data. Blood: Red blood cell count 4,360,000; white blood cell count, 12,500 with polymorphonuclear neutrophiles, 63 per cent; lymphocytes, 26 per cent; monocytes, 8 per cent; eosinophiles, 2 per cent; basophiles, 1 per cent; reticulocytes, less than .5 per cent; and platelets, 300,000. Blood Wassermann and Kahn reactions, negative; blood sugar, 95 mg. per cent; urea nitrogen, 7 mg. per cent. Urine analysis, including melanin determination, was negative. Roentgen examinations of the chest and left leg were normal

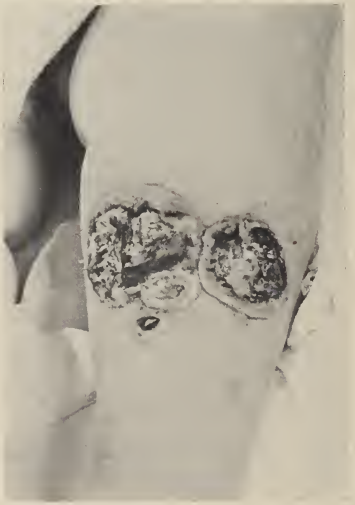

FIG. 1. Irregularly rounded ulcers with firm, elevated, nodular borders. The surfaces are covered with an adherent, greenish-black, malodorous slough.

except for the presence of diffuse calcifications in the varicose veins of the left leg. Bacteriological cultures from the ulcers showed the presence of B. coli and a green, hemolytic enterococcus. There were no fungi or higher bacteria present.

A biopsy examination on December 6, 1939 from one of the larger masses was reported as showing immature squamous cell carcinoma or amelanotic melanomatous formation. The specimen of tissue had been taken from the margin of the lesion and a definite histological diagnosis could not be made.

Course. The patient was given a high vitamin, high caloric diet. A cradle was placed over the left leg and wet dressings of potassium permanganate were applied. Radiotherapy of high voltage and moderate filtration (140 K. V. and ½ mm. of copper) was instituted immediately to the largest growth and the patient received 100 "r" units daily for nine days, 300 "r" units daily for the next nine days and thereafter, 300 "r" units daily.

The base of the ulcer sloughed out and healing gradually occurred. The other growths were treated with several courses of 300 "r" units daily until a total of 3000 roentgen units had been administered. In January 1940, another biopsy examination disclosed acute and chronic inflammatory reaction with no evidence of tumor formation. Under treatment, the ulcerations appeared cleaner and lost their foul odor but their margins showed greater infiltration. The patient was discharged in April 1940.

Second Admission. Two months after her discharge the patient complained of severe pain in the left leg and was readmitted to the hospital on May 6, 1940. The lesions were larger in size, with hard, indurated borders. The expanding character of the lesions obviated the possibility of spontaneous healing. Accordingly, amputation of the leg was performed with closure of the anterior and posterior flaps of the wound margins. The report on the pathology was: "Extensive ulceration of the skin; fibrosis and local calci-

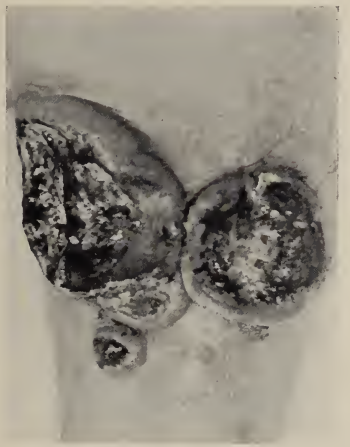

FIG. 2. Increased photographic magnification of the tumors of the leg

fication of the corium and subcutaneous tissue with conspicuous endarteritis and endophlebitis." Apparently, no tumor cells were found. Thus, although the tumor cells had been destroyed by means of radiotherapy, the lesions continued to increase in size. Healing of the incision proceeded very slowly. The wound was finally closed by granulation tissue on July 30, after seven weeks in the hospital and the patient was discharged the next day.

The patient was last seen on February 6, 1941. At that time her general condition was good. The incisional scar was well healed and firm. There was no evidence of inguinal adenopathy or of metastases in other regions of the body.

COMMENT

This case presents many problems in diagnosis which not even histopathological studies can completely solve. The clinical picture, fortified by the biopsy

examinations, limits the possibilities to two conditions, namely, immature squamous cell carcinoma and amelanotic melanoma.

Squamous cell epithelioma: This cutaneous lesion has been so frequently described that repetition is unnecessary. The fully developed tumor of the papillary type presents a cauliflower appearance and often secretes a malodorous fluid. Ulceration and crust formation are common. The edges of the growth are characteristically thickened and indurated. The most common sites are the face and neck, particularly the lip. The microscopic appearance with typical "prickle-cell" and epithelial pearl formations is characteristic. As in this case, the lesion is extremely radiosensitive and is usually completely destroyed by adequate radiotherapy.

Amelanotic melanoma: The occurrence of this type of melanoma is not generally known or recognized. These tumors usually appear on the legs following irritation of a preexisting verruca or nevus. They are frequently removed without consideration of their potential harmfulness, and subsequently recur rapidly and metastasize to the regional lymph nodes. Their behavior is very similar in effect to that of malignant melanomas. Broders and McCarty (3) state that melanotic and nonmelanotic tumors belong to the same family and differ merely in the amount of pigment. They apparently have the same cell structure as that seen in the nonpigmented areas of melano-epitheliomas and would probably produce melanin if allowed to differentiate far enough. Melanin production is presumably a form of differentiation and the absence of pigment in these tumors is evidence of such rapid growth as to prevent this melanin formation. The malignant changes unusually begin in the basal cell layers of the rete malpighi. It is well known that primary melanotic tumors may be pigmented and their secondary growths nonpigmented or only partially pigmented. There is no relationship between the amount of pigment and the degree of malignancy and both forms have an extremely poor prognosis. These growths usually occur in patients past fifty years of age and appear on the foot in the majority of cases (4). Melanuria is frequently observed although it was not present in this case.

The diagnosis can be confirmed only by histological examination. The microscopic picture is one of diversely shaped, undifferentiated cells with frequent mitotic figures. The histology of an immature squamous cell carcinoma is somewhat similar. Microscopically, amelanotic melanoma has also been confused with round cell sarcoma, fibrosarcoma, myxomatous carcinoma and endothelioma. The differential points in this case include the fact that there was no history of a traumatized growth, regional adenopathy was absent, and the growths were present on the leg rather than on the foot. There was also the marked response, at first, to radiation therapy. In this respect, the lesion behaved like a squamous cell carcinoma. However, this early response was later followed by the enlargement of the lesions and the appearance of new tumors. Inasmuch as the histological examinations were not of sufficient clarity to afford a specific diagnosis, it must be assumed that the lesions were composed of radioresistant, amelanotic melanomatous cells. The immaturity and undifferentia-

tion of these cells were responsible for the difficulty in differential histological diagnosis. It is of interest that no tumor cells were found in the final pathological specimen although the lesions had grown in size and number. It is possible that this increase in size was due to edema and connective tissue formation but this would not explain the appearance of new lesions.

It is to be emphasized that this type of growth usually follows the cosmetic removal of so-called benign verrucae and nevi. The needless irritation and stimulation of these lesions by the inexperienced and the inexpert is fraught with danger. The treatment is essentially prophylactic and should only include removal of the tumor when growth is rapid, when pigmentation is developing, or when trauma cannot be eliminated.

In addition to these two lesions there are other cutaneous lesions which may produce a similar clinical picture and which must be considered in the differential diagnosis.

DIFFERENTIAL DIAGNOSIS

Cutaneous lesions of the legs consisting of tumors and ulcers resembling those observed in this case may be encountered in other diseases, namely: tuberculosis verrucosa cutis, syphilis, sporotrichosis, Hansen's disease (leprosy), blastomycosis, coccidioidal granuloma, iododerma and bromoderma, lymphoblastoma, mainly: (a) granuloma fungoides; (b) leukemia; (c) Hodgkin's disease; Kaposi's multiple idiopathic hemorrhagic sarcoma; Darier-Roussy sarcoid (tuberculosis indurativa).

Tuberculosis verrucosa cutis: This cutaneous lesion is a localized growth due to tuberculous infection. It consists of bean to palm-sized plaques, brownish-red in color and covered with numerous papular and verrucous elements. The surface may ulcerate and become covered with crusts. The advancing borders are inflammatory, firm and steep, and small secondary abscesses may be seen beyond the periphery. Unlike the lesion described here, the surface is usually covered with crusted, horny excrescences, although exuberant, soft vegetations have been observed. In addition, this condition may be bilateral, symmetrical and leave smooth, scaling scars on involution. There may be other manifestations of tuberculosis and the tubercle bacilli may be found in the lesion. The histology is typically tuberculous.

Syphilis: Several types of syphiloderm may resemble this lesion. The ulcerative nodular syphiloderm usually develops after the first year of spirochetal infection. It consists of multiple, firm, dull-red nodules, usually grouped in a crescentic or reniform manner. The nodules may ulcerate and develop thick, superimposed crusts, purulent secretions, deep bases and sharp, clean-cut margins. The eruption is confined to one region of the body, as the face, the buttocks and the lower extremities. The massive gummatous syphiloderm is a late syphilitic lesion. Here again, one or several painless, subcutaneous tumors undergo ulceration. The secretions are thick, the floor is flat and concave, and the edges are 'punched out.' Fistulae may be present and extend deeply to the bone. Crusts may be superimposed on one another in a layered arrangement to

form an oyster shell or rupial syphilide. The scars are usually thin and delicate. Unlike the present lesion, the Wassermann reaction is positive and there are other manifestations of syphilis. Other differential points are the reniform outline, the 'punched-out' borders and the typical scars. The histological picture presents the characteristic vascular changes of syphilis. Antisyphilitic treatment may be of value as a therapeutic test.

Sporotrichosis: This uncommon infection begins as a primary nodule or an open wound and spreads rapidly via the lymphatics. The secondary lesions consist of subcutaneous nodules, abscesses and ulcers in a chain-like arrangement rather than in a group as in the case described here. The tumors are hard, tender and may ulcerate and discharge a thick, yellow pus. The organisms are not found by direct smear but may be isolated by laboratory culture and by animal inoculation. Potassium iodide is a specific therapeutic agent.

Hansen's disease (leprosy): The tubercular type of this disease may present cutaneous nodules resembling the lesions in this case. Several points are of value in differential diagnosis. There may be sensory changes with areas of anesthesia. Adenopathy and involvement of the conjunctiva and larynx are common. Spontaneous amputations of the digits and associated neurological manifestations are often seen. Cutaneously, there may be depigmented macules, with surrounding hyperpigmentation. These macules are often anesthetic but may be hyperalgesic. Leathery, mica-tinted cicatrices are common, as is alopecia and deformities of the nails. The nodules are coppery-red, waxy or varnished in appearance. They are most frequently seen on the face and impart to it a leonine expression. Finally, leprosy may be excluded by the histopathological findings and the presence of the bacilli in the nasal secretions, discharges from the ulcers and stained tissues.

Blastomycosis: The fully developed characteristic plaques are palm-sized or larger, with sloping abrupt borders covered with minute abscesses. Some of these may be crusted and discharge seropurulent fluid. The deep indolent gummatous type of blastomycosis may resemble the tumors in this patient but are not of the same consistency. They are softer, more inflammatory and tend to pursue a course with periods of progression and regression, and often heal with scar formation. Other differential points include the discovery of the specific organism in the cells, by smear as well as by culture and animal inoculation methods. The blastomyces are doubly contoured, highly refractile bodies.

Coccidioidal granuloma: Coccidioidal granuloma is uncommon in this part of the country and more commonly involves the lungs, the bones and the central nervous system as well as the lymph nodes. The ulcerated nodules are most frequently observed in adult male laborers, on the skin of the exposed parts such as the hands and arms. The indolent nodules tend to suppurate and form necrotic gummatous lesions with numerous sinuses. The tumors are also softer than those in this case and may show spontaneous involution. Finally, microscopic study of the tissue, identification of the yeast-like organism in pus and other fluids, animal inoculation and intracutaneous tests with coccidioidin readily differentiate this disease from the neoplasm described here.

Iododerma and bromoderma: The development of fungating, papillomatous and flat elevations following iodide or bromide ingestion, is not uncommon. These lesions may be several inches in diameter, brownish-red or purple in color, ulcerated, and may have punctiform abscesses on their flat upper surface. Fungating ulcers are more apt to occur on the lower extremities. However, there is usually a history of the ingestion of bromides or iodides in the form of iodized salt or as drugs. They are commonly encountered in epileptics or syphilitics under treatment, are frequently associated with a papular or pustular acneform eruption, especially on the face and upper part of the trunk and tend to disappear when the halogens are omitted. Finally, iodides and bromides are demonstrable in the urine.

Lymphoblastoma: The lymphoblastomas, especially granuloma fungoides, leukemia cutis and Hodgkin's disease, present tumors of the skin that may simulate the lesions observed in this case. As a rule, the tumors occurring in the lymphoblastomas are accompanied or preceded by generalized intense pruritus and other cutaneous manifestations of a toxic nature such as urticaria, purpura and dermatitis.

(*a*) *Granuloma fungoides d'emblée:* This uncommon variant of mycosis (granuloma) fungoides is characterized by the rapid development of mushroom-like tumors on the skin independently of the usual earlier two stages (eczematoid or prefungoid and infiltrative). The tumors develop rapidly, reach a given size and usually involute by absorption or by ulcerative necrosis. Unlike the present lesions, the tumors are shaped like tomatoes rather than elevated saucers. The base may even be sessile. The usual sites include the face, groin, axilla and chest. The involved areas often show pigmentation and necrosis and may be markedly pruritic. Adenopathy may be seen and a marked eosinophilia is present. Roentgen therapy in fractional doses causes a comparatively rapid involution. The histopathology of the tumors is distinctive.

(*b*) *Leukemia cutis:* The typical lesions are purplish or brown, glistening tumors varying in size from a kidney bean to an egg. The usual sites are the face and the extremities. In contradistinction to the present eruption, the tumors do not break down and often disappear spontaneously. The centers are depressed, with telangiectatic vessels at their borders. Infiltration may also be present in the mouth, especially in the tongue and tonsils. In addition, the tumors are usually bilateral; there is an associated glandular adenopathy and the spleen is enlarged. Pruritus is often severe. The blood picture is the final and characteristic diagnostic finding, although nodules have been noted in aleukemic dyscrazias. The microscopic examination discloses characteristic changes.

(*c*) *Hodgkin's disease:* This condition frequently occurs in association with pruritus and prurigo-like papules but occasionally nodules, tumors and ulcers are present. The lesion may be differentiated by the severe pruritus, the generalized adenopathy and the lymphatic involvement. The Gordon test is of value. The histopathology is frequently characteristic and includes the demonstration of eosinophiles, epithelioid and Sternberg-Reed giant cells in the tissues.

Kaposi's multiple idiopathic hemorrhagic sarcoma: The brownish and bluish-

red tumors of Kaposi's sarcoma may resemble the tumors in this case. However, they tend to be more prominent on the feet rather than on the leg. They are usually bilateral and may occur on the trunk, face, and mucous membranes. Suberythema doses of x-ray therapy tend to favor absorption of the tumors. The lesions in this case showed no tendency to spontaneous involution as may be observed in Kaposi's sarcoma.

Darier-Roussy sarcoid (tuberculosis indurativa): This subcutaneous granuloma is usually composed of several walnut-sized nodules. Unlike the lesion described here, the tumors are globular or oval and freely movable. They may coalesce to form deep, irregular plaques in which the overlying skin resembles orange-peel when pinched. The color is usually purplish-red and the most common site is the trunk. The course is slow and prolonged, and ulceration is uncommon.

THERAPY

The early response of this tumor to radiation therapy with the subsequent appearance of new lesions, brings up the question of the value of roentgen rays in cutaneous malignancies. It is well known that lymphatic, embryonal and physiologically active cells, especially those undergoing mitosis, are sensitive to radiation. Ewing classifies tumors in decreasing order of radiosensitivity as follows: 1) lymphomas; 2) embryonal tumors; 3) cellular anaplastic tumors; 4) basal cell carcinomas; 5) adenomas and adenocarcinomas; 6) desmoplastic tumors; 7) fibroblastic sarcomas and neurosarcomas. He grades them further on their histologic structure as follows: 1) squamous or prickle-cell carcinoma, radioresistant; 2) transitional cell carcinoma, highly malignant and radiosensitive; 3) basal cell carcinoma, comparatively benign and radiosensitive; 4) lympho-epithelioma, highly malignant and radiosensitive. Although the histological structure is of great value as a guide in prognosis and determination of the response to radiation, the clinical picture must always be carefully considered. Innumerable factors, such as age, location, vascularity, constitutional status and heredity, may greatly influence and modify the effects of therapeutic irradiation. In this patient, the histological section showed immaturity and undifferentiation of many cells which should suggest radiosensitivity of the tumor. However, the clinical features and the histological resemblance of the tumor to an amelanotic melanoma would presuppose radioresistance. Accordingly, the lesions responded, at first, to radiotherapy. However, new lesions eventually appeared and amputation of the extremity was necessary. The histological picture cannot be divorced from the clinical findings, but it should not be considered an absolute criterion when advancing a prognosis.

SUMMARY

1. An unusual case of malignant tumors and large ulcers of the leg in a woman is reported.

2. The histopathologic studies made prior to the institution of treatment revealed evidence of immature squamous cell carcinoma and amelanotic melanoma.

3. The differential diagnosis of the lesions from simulating cutaneous diseases and growths is discussed.

4. Following intensive roentgen-ray therapy there was temporary retardation of growth and partial involution of the tumors.

5. Amputation became imperative because of extension of the ulcers and the occurrence of intense pain.

6. Examination of the tissue after amputation revealed no further evidence of malignant growth, probably as a result of the intensive roentgen-ray therapy.

7. A final examination in February, 1941 showed no evidence of regional adenopathy or of metastases in other regions of the body.

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ABSCESS OF THE FRONTAL LOBE SECONDARY TO FRONTAL SINUSITIS

Operation and Recovery

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The following case merits description because of the rapidity with which an acute frontal sinusitis, accompanying a mild upper respiratory infection was followed by the development of a brain abscess in the frontal lobe. Of interest also is the postoperative course, during which signs of meningitis developed, and a routine x-ray examination of the skull revealed the spontaneous accumulation of air in the ventricular system. In spite of all these complications, the patient made a full recovery.

CASE REPORT

History (Adm. 463757). T. D., a man, aged 24 years, was admitted to the hospital on October 11, 1940. He had been well until the recent illness. Ten days before admission he contracted a mild upper respiratory infection and several days later began to suffer severe headache over the right eye. Motion of this eye was somewhat painful.

Examination. On entering the hospital his temperature was found to be 103°F. and his pulse rate was 96 per minute. The neurological status was negative except for nuchal rigidity and tenderness over the right frontal bone of the skull. The upper lid of the right eye was somewhat swollen. Purulent discharge was seen in the right nostril. The right middle turbinate was polypoid. X-ray studies disclosed a right pansinusitis. The white blood count was 14,000 of which 75 per cent were polymorphonuclear leucocytes. A lumbar puncture yielded bloody cerebrospinal fluid, which contained a rather high white blood count (200 white blood cells of which 75 per cent were polymorphonuclear leucocytes). Blood culture was negative.

The diagnosis of empyema of the right frontal sinus with meningeal irritation was made.

Operation. An external operation (Riedel type) on the right frontal sinus was performed under local anesthesia. An empyema of the frontal sinus was found. The mucosa was thickened, especially in the region of the nasofrontal duct. The polypoid mucous membrane was markedly swollen in this area, causing an obstruction of the duct. On removal of the posterior wall of the sinus, a large epidural abscess was encountered. The dural wall of the abscess was thick and did not pulsate. This epidural abscess extended laterally and posteriorly (over the roof of the orbit) for about one inch, at which point a fistula was noted. This, on further investigation, was found to lead into a brain abscess.

The floor, the anterior wall, and the posterior wall of the frontal sinus were then removed. Sufficient frontal bone and roof of the orbit were resected to expose the abscess. A small sized Mosher drain was inserted after packing off the meninges. No sutures were used and the wound was left open. Throughout the operation the patient was conscious and somewhat euphoric. He was placed on sulfanilamide therapy, grains 20 every four hours. Fluids were restricted. The sulfanilamide was continued, except for short intervals, for about five weeks.

Pathological report on the biopsied mucosa revealed "acute inflammation." Cultures from both the nasal secretion and the brain abscess showed streptococcus, H. beta, and staphylococcus.

Postoperative Course. During the first four days following the operation there was satisfactory progress, but on the fifth day there was a rise in the white blood count to 20,000

and two days later signs of meningitis appeared. The temperature rose to 104°F. and a lumbar puncture revealed a four plus Pandy reaction and 3,000 white blood cells of which 40 per cent were polymorphonuclear leucocytes. No bacteria were found in the cere-

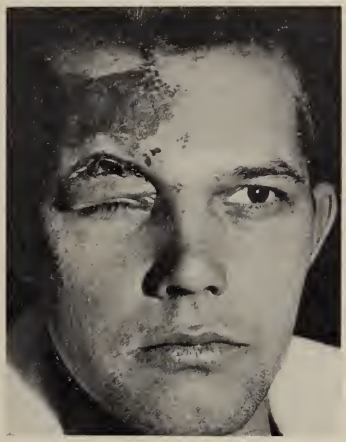

FIG. 1. Two weeks after operation. Note Mosher drain still in place

FIG. 2. Three and a half weeks after operation. Note air in ventricles

brospinal fluid. Under continued chemotherapy, consisting of 200 cc. of 0.8 per cent sulfanilamide administered intravenously every four hours, the sulfanilamide reached a concentration of 13 mg. per cent. The patient's condition began to improve within 24 hours.

The packings were removed ten days after operation (fig. 1), and the Mosher drain was removed two weeks later. Improvement continued with no untoward events, except for the finding of air in the ventricles on a routine x-ray examination of the skull (fig. 2). This was thought to indicate the presence of a communication between the abscess cavity and the adjacent cerebral ventricle. However, it gave rise to no detectable clinical symptoms. Subsequent x-ray examinations showed prompt disappearance of the intraventricular air.

At the end of five weeks of sulfanilamide therapy, the blood count showed that the white blood cells had dropped to 4,400, although no clinical symptoms of toxicity were noted. The blood count, however, returned to normal three days after the administration of sulfanilamide was stopped. The dressing was removed and the patient was allowed out of bed six weeks after the operation.

DISCUSSION

Within ten days after a mild rhinitis a patient developed an abscess of the frontal lobe complicating an empyema of the frontal sinus. With the exception of a transient meningitis, recovery was uneventful and occurred in six weeks. The finding of air in the cerebral ventricles on x-ray examination suggesting the possibility of a communication with the abscess was an accidental discovery, but there were no untoward symptoms of this spontaneous pneumoencephaly.

Eleven cases of frontal lobe abscess (secondary to frontal sinusitis) have been observed in this hospital during the past ten years. All of these were operated upon by the several surgeons of the hospital; five of the eleven recovered. In a series of forty cases of similar lesions operated upon both in this country and abroad, only seven recovered (1, 2). The usual mortality is about 85 per cent (Hagerup (5) reports twelve rhinogenous abscesses with eleven deaths); while at our hospital the mortality is about 55 per cent.

As is well known, frontal lobe suppuration may show few symptoms, since focal signs are often lacking. However, given a case of frontal sinusitis with a sudden change for the worse (without there being evidence of a meningitis or of an osteomyelitis to account for such an exacerbation), the possibility of a frontal lobe abscess must be considered. If there are, in addition, psychic changes, the probability of such an abscess is greater.

Of significance in this case is the rapidly developed well encapsulated abscess—only ten days after the onset of a mild rhinitis did encapsulation take place. Usually, the period of anticipated encapsulation is about four weeks (3, 4). This interval is often characterized by improvement in the general condition, a fall in temperature, papilledema becoming stationary, and the polymorphonuclear leucocytes in the cerebrospinal fluid being replaced by lymphocytes. Sometimes, however, a rising temperature, and an increasing papilledema may necessitate earlier intervention. Apparently, in the type of case under discussion an early retrograde thrombophlebitis takes place with rapid walling off and fistula formation.

It is fairly generally accepted that unless a lead into the abscess is found during the operation on the frontal sinus, it is best to operate through a clean area. If, however, such a lead is found, a radical frontal operation followed by drainage of the abscess, preferably by means of the Mosher drain (6) is more advisable.

Thanks are due to the Neurosurgical Service of Dr. Ira Cohen for its constant cooperation.

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GIANT HYPERPLASIA OF THE GUMS FROM DILANTIN SODIUM

LEO STERN, D.D.S. AND LEON EISENBUD, D.D.S.

[*From the Neurological Service and the Dental Clinic*]

Hyperplasia of the gums as an occasional side reaction to dilantin-sodium therapy is receiving extended comment in recent literature. The classical picture is one of massive gingival hypertrophy with underlying edema. It is probable, however, that subtler changes occur more frequently, and that they are overlooked, particularly by the clinician who is not thoroughly familiar with the appearance of the normal periodontal tissues. Thus, in four recent reports, the incidence of gingival alterations resulting from dilantin therapy vary from 6 per cent to 62 per cent (Table I).

The significance of this reaction is obscure. Kimball found an association of subvitaminosis C with hyperplasia, and as a control, normal ascorbic acid levels in unaffected patients. Frankel's figures concur. Yet Gruzhit (5) concluded, on the basis of animal experiments, that dilantin does not affect the utilization of vitamin C.

An eosinophilia of moderate degree occurs in a few patients who exhibit both hyperplastic gums and cutaneous manifestations, but other consistent changes in blood cytology have not been recorded. Neither age nor dosage appear related to oral reactions.

In the dental literature, Thoma (6) noted bilateral dental cysts in an affected patient. Glickman and Lewitus (7) found no predisposition to this complication in patients who had heavy deposits of dental calculi. The possible role of other local factors, such as preexisting gingival disease or the traumatism of an overstressed bite, have not been studied.

The following case of massive gingival hypertrophy following the administration of dilantin presents several interesting features in the medical and dental work-up.

CASE REPORT

History. (Adm. 33-20373). M. R., a 17 year old Negress was referred to the dental clinic from the neurological service, where she was under treatment for idiopathic epilepsy and marked mental retardation in 1933. Radiographs disclosed many abscessed teeth, which were extracted.

In 1936 she returned to the dental department for further treatment and several more teeth were extracted. At this time clinical note was made of the presence of a hypertrophic gingivitis due to traumatic occlusion (overstressed bite) with a complicating Vincent's infection. Conservative periodontal treatment was instituted, instruction in mouth hygiene was given, and subsequently the patient was discharged.

Until late in 1939 the patient had been receiving phenobarbital. On November 13, 1939 dilantin-sodium therapy was begun and one month later it was noticed that the gum hyperplasia had become aggravated. The soft tissues about the teeth continued to grow rapidly thereafter.

In January 1941 the administration of the drug was discontinued in an effort to check the gingival expansion. Some improvement and shrinkage of the tissues was noted during the

ensuing month, but because of the increased frequency of epileptic seizures, dilantin was prescribed.

Dental Examination. The gum margins both labially and lingually were raised above the gingival line to a level that covered over half of the tooth-crowns, rising in scalloped, sessile masses from an edematous base (fig. 1). The tissues were dark pink, glossy and lobulated. The greatest change occurred in the region of the lower anterior teeth. There was extensive proliferation about the other teeth as well, even for a short distance on the edentulous areas beyond the teeth. No spontaneous bleeding was observed, but excision

TABLE I

Reports of Hyperplastic Gingivitis Following Dilantin Therapy

BIBLIOGRAPHIC REFERENCE	AUTHOR	TOTAL CASES REPORTED	CASES SHOWING REACTION	PERCENTAGE
1	Merrit, H. H. and Putnam, T. J.	142	8	6
2	Fetterman, J. L.	28	7	25
3	Kimball, O. P.	119	68	57
4	Frankel, S. I.	48	30	62

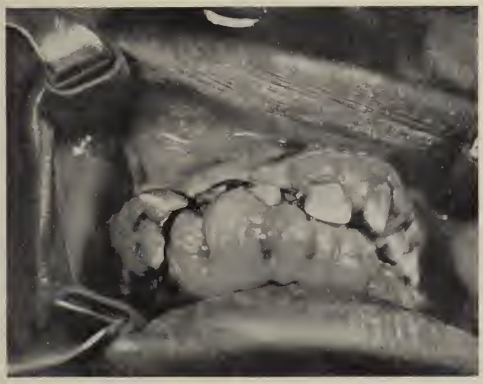

FIG. 1. Clinical picture of giant hyperplasia of the gums

for biopsy resulted in more profuse hemorrhage than that encountered in cutting normal tissue. The soft-tissue proliferation had caused considerable displacement of the teeth. The saliva was of normal consistency but excessive in quantity.

Microscopic Examination. A block of tissue $\frac{1}{2}$ x $\frac{1}{4}$ inch was excised, cutting directly to the alveolar bone, from the lingual side of the lower incisors. Stained sections showed striking acanthosis and hyperkeratosis, increased fibrous tissue and infiltration of plasma cells (fig. 2).

Laboratory Data. The vitamin C level of the blood was 0.67 mg. per cent. Hemoglobin, platelets and white cell count were normal except for a lymphocytic differential of 40 per cent. The Wassermann reaction was negative.

X-ray examination revealed the skull to be dolicocephalic in type with marked thickening of the bones of the calvaria in the parietal and occipital regions. The sella turcica was normal. Many carious teeth were demonstrated in the dental radiographs, but no evidences of bone abnormality appeared other than retarded calcification of the post-extrac-

FIG. 2. Section of excised gum tissue. Note increased thickness of fibrous tissue layer and hyperkeratosis.

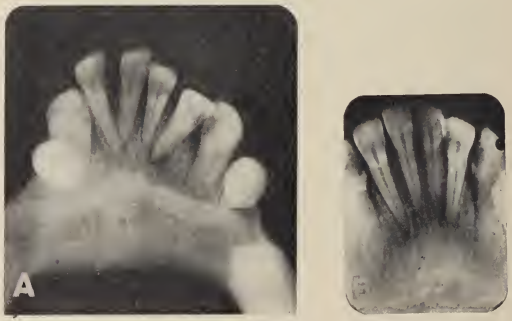

FIG. 3. Radiographs showing the amount of displacement of the lower anterior teeth. (A) 1941, (B) 1936.

tion sockets. Considerable lateral displacement of the lower incisors was indicated in a comparison of these with the radiographs made in 1936 (fig. 3).

DISCUSSION

In reviewing this case several points deserve discussion. The degree of gingival reaction in the patient was far greater than that observed in any other

among a large group examined in the neurologic clinic, and greater than that demonstrated in published photographs accompanying other case reports.

A tendency towards hypertrophic gingivitis had been noted as far back as 1930. At that time the normal interlocking bite relationship of the teeth was disturbed and unquestionably the extraction of several teeth caused further malocclusion. It is accepted that traumatic masticatory stresses from malposed teeth invariably produce inflammatory changes in the periodontium. It is fair to assume that in this case, the malocclusion offered a *locus minorus resistentiae.*

The relationship of subvitaminosis C to the gingival hypertrophy has not been conclusively discounted in our minds, since the ascorbic acid reading of 0.67 mg. per cent is a low normal. Furthermore, the free bleeding which followed excision for biopsy was strongly suggestive of a hemorrhagic tendency.

The significance of the high lymphocyte count is obscure, but is noted for the record. In the absence of an enlarged pituitary gland, the spreading of the lower teeth indicates the infiltrating character of the hyperplastic tissue.

In contrast to the clinical picture described, the nonulcerative hyperplasias of the gums encountered in riboflavin deficiency, early scurvy, pregnancy, and following the administration of progynon are moderate in extent and characterized by tendencies towards livid discoloration and spontaneous bleeding. Rapid involution generally follows removal of the cause or supply of the deficiency. Nevertheless, an occasional hyperplastic reaction of the gums to estrogenic hormone therapy presents both clinical and histopathologic resemblances to the milder reactions following dilantin therapy. This similarity suggests an interesting line of investigation.

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CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

Wednesday, January 10, 1941

Bacteria-free Course of Subacute Bacterial Endocarditis. Death from Hemolysis of Apparently Compatible Transfused Blood.

[*From the Medical Service of Dr. George Baehr*]

History (Adm. 441848; P.M. 11277). A white woman, aged 37 years, was first admitted to this hospital August 1, 1928 complaining of right lower quadrant pain. A supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed for a right tubo-ovarian abscess and a left salpingitis. At that time no cardiac abnormalities were found; the blood pressure was normal; no abdominal viscera were palpable; the urine was negative. She was discharged on August 23, 1928.

Second Admission. The patient was readmitted to the Gynecological Service April 17, 1939 because of frequency, urgency and nocturia. Examination revealed a loud, rough, apical, systolic murmur. The basal metabolic rate was plus 26 per cent, but this was probably due to an intercurrent illness. The sedimentation time was 39 minutes. The urine showed one plus albumin. The temperature ranged up to 100.8°F. She was discharged three days later because of the absence of any gynecological disease without adequate investigation of the cardiac condition.

Interval History. One month later she was seen for the first time in the Medical Clinic of the Out-Patient Department, complaining of pains in the shoulders and arms. The liver edge was palpable three finger-breadths and the spleen two finger-breadths below the costal margin. No cardiac murmurs were heard. One month later, the same examiner noted a loud systolic and presystolic murmur at the apex. Secondary anemia and albuminuria were present.

Third Admission. At this time (June 12, 1939) she stated that for the past six years she had experienced some dyspnea on moderate exertion. Aside from increased urinary frequency and urgency during the previous two years, she had been well until one and a half years before admission. At that time she began to have drawing pains in her arms and legs which occurred intermittently. Recently these pains have become more intense. During the last few weeks before admission, weakness had been marked enough to keep her in bed. For six months there had been an occasional burning sensation beneath the upper portion of the sternum. This occurred when walking, and forced her to stop and rest. Three weeks before admission she noted for the first time a choking sensation in the throat, accompanied by dyspnea. The latter was most marked at night. In addition, a sharp, cutting, non-radiating pain had appeared in the left side along the costal border.

Examination. The patient was well developed and well nourished, in no apparent distress. The sclerae were muddy. The neck veins were prominent. Bilateral bean-sized axillary nodes and shotty inguinal nodes were palpable. The lungs were clear. The heart showed a moderate enlargement to the left. There was a faint apical systolic thrill. The sounds were of good quality. A loud, rough, systolic murmur was heard over the precordium, and was not transmitted to the neck or back. P_2 was louder than A_2. There was a regular sinus rhythm. The blood pressure was 110 systolic and 70 diastolic. The abdomen was soft. A smooth, slightly tender liver edge was felt two finger-breadths below the costal margin. A smooth, slightly tender spleen descended three finger-breadths below the costal margin. There was no ascites or clubbing. Neurological examination was negative.

Laboratory Data. Blood: Hemoglobin, 66 per cent; red blood cells, 3,820,000; white blood cells, 3,400 with 48 per cent polymorphonuclear leucocytes; 43 per cent lymphocytes; 8 per cent monocytes; and 1 per cent basophiles. Platelets, 210,000; reticulocytes, 1.2 per cent. Sedimentation time, 24 minutes. Venous pressure, 5.5 cm. Saccharin time, 10 seconds. Vital capacity, 1900 cc. The urine showed a specific gravity of 1.027, contained a trace of albumin, no sugar, and a rare red and white blood cell. Blood chemistry: urea nitrogen, 17 mg.; sugar, 100 mg.; cholesterol, 200 mg.; calcium 9.7; albumin 4.6; globulin, 2.6; total protein, 7.2 gm.; icteric index, 4; Takata Ara, 4 plus. The Wassermann reaction was negative; blood culture showed no growth. Agglutinations against Brucella, typhoid, paratyphoid and dysentery organisms were negative. Galactose tolerance test was normal. Electrocardiogram showed a left axis deviation, prominent P waves, slightly slurred QRS, depression of R-T in leads I and II, T_1 deeply inverted, T_2 diphasic, and T_4 inverted. Subsequent electrocardiograms showed no change. X-ray examination of the chest revealed a moderate enlargement of the left ventricle. X-ray examination of the long bones showed no abnormality. Ear smear revealed the presence of a large number of macrophages ranging from 5 to 10 per cent.

Course. Throughout her course the patient was febrile, the temperature ranging between 100 and 102°F. The urine consistently showed a trace of albumin, 1 to 4 red blood cells per high power field, occasional white blood cell, hyaline and granular cast. Intravenous pyelography and cystoscopy showed no evidence of disease of the urinary tract. On three occasions she complained of small amounts of bleeding from the perineum; this was never objectively verified. She complained bitterly of pain in the extremities, pain in the back radiating around the left costal margin, and attacks of pain beginning in the left shoulder and radiating down the left arm to the hand and fingers. During the latter attacks of pain there were no objective findings except on one occasion when a tachycardia of 124 was noted.

Two months after admission she developed a tender hemorrhagic spot on the sole of the left foot which did not fade on pressure. It disappeared very slowly. One observer recorded this as an Osler node. Her condition gradually deteriorated. The anemia persisted and progressed in spite of several blood transfusions. Numerous blood cultures were negative. In addition the leucopenia persisted; at one time the white blood cell count dropped as low as 1500 with only 12 per cent polymorphonuclear leucocytes.

The patient remained a diagnostic problem. The possibility of subacute bacterial endocarditis arose immediately in view of the fever, splenomegaly, anemia, cardiac murmur, presence of macrophages, and urinary findings. However, repeated blood cultures were negative. It was believed by some that the spleen was entirely too large for this disease, nor would the diagnosis account for the hepatomegaly. The persistent leucopenia, anemia, thrombocytopenia, lymphocytosis, monocytosis in the peripheral blood, and the presence of maturation arrest of the myelocytic series in the bone marrow suggested to the hematologists a disease of the reticulo-endothelial system rather than subacute bacterial endocarditis. During the four months after admission she steadily declined, at times being drowsy, other times uncooperative, always complaining of pain. She was given another transfusion. One-half hour later she developed a severe shaking chill, the temperature

rose rapidly to 107.4°F. and she developed hemoglobinuria. She soon became comatose. In spite of vigorous therapy, pulmonary edema developed and she died within ten hours after the transfusion. Recheck of the blood groupings confirmed the compatibility of the two bloods, both being of Group I.

Necropsy Findings. The *heart* showed definite evidence of an old rheumatic valvulitis. The entire free flap of the mitral valve was distinctly thickened. The chordae, at the points of insertion, were also thickened and were devoid of the normal web-like insertion. In addition there was a small, distinct, flat, ulcerated lesion on the valve. On the aortic ostium between the leaflets and the anterior commissure there was also a small ulcerated lesion. The ventricular aspect of the aortic cusps was thickened. Crushings from these lesions were negative. The *spleen* was enlarged, but no infarcts were present. No gross infarcts were present in any of the other organs. Microscopic examination of the edge of the vegetations, using a bacterial stain, showed masses of dark-staining "ghosts" of bacterial colonies. These appeared to be destroyed and in all probability no longer viable. In the *kidney* there were a few, characteristic embolic glomerular lesions.

Comment. Dr. Klemperer. This case presents the picture of a subacute bacterial endocarditis implanted on a rheumatic valve. The negative blood cultures are due to the fact that the bacteria had been spontaneously destroyed and were no longer viable.

Dr. Baehr. This case is of particular importance in helping to interpret cases treated with drugs of the sulfanilamide and sulfapyridine group which post mortem present evidences of healing. In this instance the vegetations on the valves are almost completely healed and yet no chemotherapy had been employed. I emphasize this fact because the mere presence of a healing valvular lesion is not a sufficient basis upon which to predicate any specific effect to a drug. In order to attribute any beneficial action to these drugs, the patient must be cured clinically as well as bacteriologically. Marked splenomegaly is particularly characteristic of the bacteria-free stage of subacute bacterial endocarditis, as has been pointed out by Libman. We have as yet no satisfactory explanation of the persistent splenomegaly in the bacteria-free cases and of the fact that it is often greater than in the active bacterial cases.

Dr. Rosenthal. Such marked leukopenia is rarely found in subacute bacterial endocarditis. I have observed it in only one other case. The presence of macrophages is of great interest. Although these cells are not pathognomonic, one can be reasonably sure of the diagnosis of subacute bacterial endocarditis if they can be demonstrated in the ear blood and are absent in the peripheral circulation. The occurrence of a transfusion reaction with marked hemoglobinuria and a fatal issue in spite of unquestioned compatibility of the blood of donor and recipient, remains an unexplained phenomenon. It cannot be explained by the presence of subgroups of the isoagglutinins.

Dr. Baehr. The cause of such transfusion reactions may very well lie in some peculiarity in the physical or chemical state of the blood, as in paroxysmal hemoglobinuria. Our inability to discover the cause of hemolysis after so-called compatible transfusions may be due to the fact that we have been overstressing the significance of the subgroups of the isoagglutinins. The observations of Joannovics and Pick on toluendiamine poisoning revealed that a chemical alteration may occur in the red blood cell without altering its biological proper-

ties and yet on being introduced into the body it will be promptly removed and destroyed by the spleen. In this case we have an enormous enlargement of the spleen and a diffuse disturbance in splenic function is suggested by the persistent leucopenia and thrombocytopenia. The transfused red blood cells belong to the compatible type. Therefore some undiscovered physical or chemical alteration occurred in them, which had not occurred at previous transfusions, and this change resulted in their rapid removal and destruction largely by the spleen so that hemoglobinuria and death resulted within ten hours.

Reported by *Dr. Max Ellenberg*

CLINICAL NEUROPATHOLOGICAL CONFERENCE

Joseph H. Globus, M.D., *presiding*

Monday, February 10, 1941

Case 7.[1] Metastatic Carcinoma of the Brain

[*From the Medical Service of Dr. George Baehr*]

History (Adm. 448562; P.M. 11333). M. S., a man aged 60, was admitted to the hospital complaining of loss of weight and vomiting. He was apparently well until three months before admission when he noted that he was unable to defecate as well as previously. He also began to vomit after each meal. He lost thirty pounds in weight and became so weak that he had to remain in bed. During the five weeks before admission he had severe vertex headache. Mental dullness, confusion and somnolence were noted by his daughter. Slight cough with some expectoration also occurred.

Examination: The patient was drowsy, exhibited poor memory and wept easily. He showed signs of marked, recent weight loss. There were no abnormal physical findings in the chest. The blood pressure was 135 systolic and 80 diastolic.

Laboratory Data: There was a leucocytosis of 24,900, but otherwise the blood findings were normal. X-ray examination of the skull showed numerous areas of rarefaction suggestive of metastatic malignancy. A Rehfuss test meal examination showed no free hydrochloric acid and a total acid content not higher than 30. Blood was found in almost all of the specimens. An x-ray examination of the chest was not satisfactory due to lack of cooperation by the patient.

Course: A psychiatric consultant suggested that the patient was suffering from a toxic-exhaustive state as a result of hysterical vomiting and malnutrition. A neurologic consultant discovered the following signs: bilateral moderate papilledema; right supranuclear facial weakness; depression of all deep reflexes; inconstant right Oppenheim and Babinski signs; marked weakness of the right upper extremity. A diagnosis of a metastatic neoplasm in the left cerebral hemisphere was made. The patient remained in the hospital only five days. He became increasingly lethargic, developed Cheyne-Stokes respiration and died on November 16, 1939.

Necropsy Findings. Brain. Gross: The anterior portion of the frontal bone on the left side was the seat of a flat, pinkish, fleshy nodule about 2 cm. in diameter which replaced both the external and internal tables and was slightly adherent both to the overlying galea aponeurotica and to the underlying dura mater. A similar lesion was found in the squamous portion of the left temporal bone. This measured about 0.5 cm. in diameter. The brain was dry and firmer in consistency than usual. The convolutions over the left fronto-parietal region were flattened and seemed softer than those of the opposite side. Four firm nodules were found in the cortex of the left cerebral hemisphere. They were located in 1) the posterior part of the middle temporal convolution; 2) about the center of the left central sulcus; 3) the inferior part of the left premotor area and 4) the middle frontal convolution. There was marked sclerosis of the vessels at the base of the brain. Coronal sections of the brain revealed the presence of many well demarcated nodules varying in size from about 2 mm. in diameter to about 15 mm. in diameter. They were found throughout the cortex and subcortex of the cerebrum as well as the cerebellum (fig. 20). A fairly

[1] The first six cases were presented in previous issues of the Journal (Vol. VIII, No. 3, 4, and 6; Vol. IX, No. 1).

large tumor was also found in the floor of the fourth ventricle. About twenty were counted, but this number does not exhaust the count of all the metastatic nodules that could have been found by further cutting of the brain. The individual lesion was well demarcated from the surrounding cerebral parenchyma, appeared granular and contained small areas of what appeared to be necrotic tissue.

Microscopic: A section from one of the metastatic nodules in the brain showed cells of low cuboidal type with a tendency to a compact arrangement about blood vessels (fig. 21). Areas of necrosis were found in many parts, also extravasations of blood cells and occasional perivascular lymphocytic cuffings. In the brain tissue contiguous to the tumor there were zones of rarefaction with replacement by a glial network and marked pathologic alterations in the ganglion cells.

The primary focus was found to be a carcinoma of the bronchus.

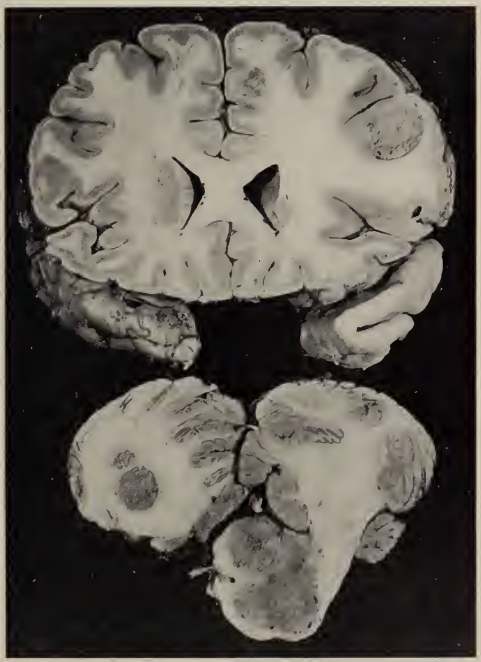


FIG. 20. Coronal section of the brain and brain stem showing a few metastatic nodules. One is seen in the left frontal lobe and two are noted in the white matter of the cerebellum while four are seen in the cortex of the cerebellum. A large one is seen in the tegmentum of the pons.

FIG. 21. Histological appearance of the metastatic nodules in case 7 (Hematoxylin-eosin, photomicrograph ×200).

Comment. Dr. Globus: A recent review of a series of 57 cases of metastatic brain tumor by myself in collaboration with Dr. Meltzer is now in press and will appear in the Archives of Neurology and Psychiatry. Many clinical and anatomical features are discussed there at great length and may serve as a commentary on this case. At this point, it is worth while to point out one significant feature—that primary carcinoma of the lung serves as the most common origin of metastatic tumors of the brain.

Reported by *T. Meltzer, M.D.*

The Story of The Mount Sinai Hospital, of which the first two installments appeared in preceding numbers of the JOURNAL, *is offered in celebration of the Hospital's ninetieth birthday. In its present form it consists mainly of historical notations which to some extent reflect the "way" of medicine in New York and elsewhere, as well as the changing environment since 1852. It has been compiled by Miss Jane Benedict from hospital records, personal and professional correspondence, medical and historical literature, and interviews with those who have been both eye-witnesses and agents of its progress. It is presented as source material from which later a more complete history is to be written.**

The first two installments were devoted to a description of the founding as well as of the founders of the Jews' Hospital of New York, the forerunner of the modern Mount Sinai.

This installment gives an account of the organization of the medical and administrative staffs of the Hospital during its first year. There is a closeup of surgery and surgeons during the transition from the pre-anesthetic era.

THE FORMATIVE YEARS, 1852-1872

III

Even before its building was completed, there had been offered to the little Jews' Hospital the services of some of the most eminent physicians of the period, offers that were of tremendous value to the struggling Society. Valentine Mott, the dean of American surgery, was among the first, in 1853, to express his readiness to serve on the Staff. He was in his sixty-eighth year, the outstanding surgeon of his day and a pioneer in vascular surgery. His teacher, Sir Astley Cooper, spoke of him as one who "has performed more of the great operations than any man living."[37] He is said to have amputated almost a thousand thighs and was the first to place a ligature around the innominate artery only two inches above the heart. At one time, in 1828, he had to tie forty arteries in a single operation which lasted four hours.[38] Such operations appear all the more astounding when it is considered that they were performed before the days of ether, with the patient fully conscious while under the surgeon's knife.

The year 1846, which preceded the incorporation of the Jews' Hospital by only six years, is of great significance for in that year ether was used for the first time in an operation performed in any hospital. Dr. J. Collins Warren operating and Dr. William T. G. Morton administering the anesthetic were the first to give a demonstration of surgery without pain at the Massachusetts General Hospital in the presence of the surgical and medical staff of that institution.

* Corrections, if errors of fact or interpretation are discovered, and additional information which may help to make the picture more complete, are welcome and may be addressed to the Historian of the Hospital.

[37] Medical Life, Jacobi Number, Victor Robinson, Vol. 35, No. 5, May, 1928.

[38] Gross, S. D.: Memoir of Valentine Mott. Lindsay & Blakiston, 1868.

With the operation successfully completed Dr. Warren, apparently sensing the need of dispelling the doubt that lingered in the minds of those in the audience, turned to them and said, "Gentlemen, this is no humbug."[39] Thus the "observant eyes and studious brain" of Crawford W. Long of Georgia; the experiments of Horace Wells of Connecticut,[40] and the tenacity of William T. G. Morton of Massachusetts made it possible for the surgeon to remove diseased tissue without causing added suffering to the patient. The terms "anesthesia" and

FIG. 1. Dr. Valentine Mott

"anesthetic," coined by Oliver Wendell Holmes, came into general usage shortly thereafter.[41]

Valentine Mott's career began some forty years before the discovery of anesthesia. The conditions under which he had been forced to operate during that time are suggested by the following excerpt from an account written in 1865—

[39] Gwathmey, J. T.: Anesthesia. Macmillan Co. 2nd Ed., p. 13, 1925.
[40] Garrison, Fielding H.: History of Medicine. W. B. Saunders Co., 1924.
[41] See footnote 39.

early enough for the pre-ether days of surgery to be still fresh in the author's mind:

"... in Dr. Mott's early days stout arms held down the writhing man, firm violence was requisite to keep proportionably quiet the shrieking child, while her neck swollen with convulsive efforts, presented but a warning obstacle to relative anatomy, and yet the trachea must be cut to save her life."[42]

The pioneer days of medicine during which Valentine Mott developed as a brilliant and careful surgeon were crowded with emergency operations that had to be performed almost on the spot where the patient was stricken. In those days when Mott began his career (newly graduated from Columbia College, 1806), a surgeon was often called upon to go the length of the city at any hour of the day or night to give aid to a critically ill patient. The time of waiting for his arrival must have been an anxious one for the patient's relatives, as the speediest transportation was the horse; the streets were badly paved and ill lit; the distances between built-up sections were great and lonely enough to threaten harm to the late traveler. To perform an operation in a hospital was a crude enough procedure in the light of our modern methods, but to operate in a patient's home presented even greater difficulties.

"Many a time had the young anatomist (Valentine Mott) been called upon to perform at midnight, by the flickering aid of a tallow candle, or the misty light of a muffled lamp, operations not only difficult in themselves and dangerous to the patient, but without any other assistance than that of excited relatives or ignorant friends. Such operations as that for hernia, the ligation of a lacerated artery or the performance of tracheotomy, have not only been attended with complete success, but afforded instant relief to the sinking sufferer."[43]

When the Jews' Hospital came upon the medical scene, such men as Valentine Mott had already seen the early crudities in medicine beginning to smooth out. They saw the chaotic conditions under which medical schools had been organized in the twenty years previous to the incorporation of the Hospital, and which persisted for some time, under which a group of physicians could establish a school with practically no supervision from the government. They would set themselves up as teachers, providing almost no equipment or adequate libraries, the teaching of medicine often being purely didactic, without any recourse to hospital material for practical demonstration or dissection for the study of anatomy. To be sure, not all the medical schools founded in the twenty years between 1832 and 1852 were of this description, but among the fifty-three that sprang up in that period there were many that had no right to exist.[44] It was to correct these conditions, among others which were producing inadequately trained physicians, that the American Medical Association was formed in 1847.

[42] Francis, Samuel W.: Memoir of the Life and Character of Dr. Valentine Mott. W. J. Widdleton, 1865.

[43] See footnote 42.

[44] Sigerist, Henry E.: American Medicine. W. W. Norton Co., 1934.

Although for some years the situation did not improve much, Valentine Mott lived long enough to see the recognition of the existing evil. A great step forward was the publication of one of the most monumental works in American medicine, Daniel Drake's *A Systematic Treatise, Historical, Etiological and Practical, on the Principal Diseases of the Interior Valley of North America as They Appear in the Caucasian, African, Indian and Esquimaux Varieties of its Population.* This publication appeared in two volumes, in 1850 and 1854, a contribution which was remarkable for a man who had never been outside the

FIG. 2. Dr. Benjamin W. McCready

United States and who had received his medical education in this country while many of his contemporaries went abroad for part of their training.

Valentine Mott himself, after having been graduated from Columbia College, spent three years in England and on the continent, ". . . the facilities for acquiring accurate and clinical information in this city (New York) being almost altogether confined to jails, almshouses and prison ships; besides being under the supervision of unprincipled, ignorant politicians who in most cases, sacrificed the lives of the deceased to the acquirement of unmerited gains."[45] Such was

[45] See footnote 42.

the situation forty years before the Jews' Hospital was founded; it was the same period during which Daniel Drake trained himself in this country, but matters had improved somewhat by 1852. Drake's book, besides being the first encyclopedic account of the climate, geography, and population of the United States, particularly in the West, stressed the relationship of these conditions to disease. It was the first introduction to public hygiene. Drake died in the year the hospital was founded.

Valentine Mott's generation had also witnessed the work of William Beaumont who died the year after the Hospital was organized. His chief work was a contribution to physiology which appeared in 1833 and recorded his *Experiments and Observations on the Gastric Juice and the Physiology of Digestion*. This was the result of 238 experiments carried on through a fistula in the stomach of a man who had been wounded accidentally by a discharge of buckshot.[46] Great advances were also made possible in the field of gynecology through the discovery by James Marion Sims, an Alabama physician, who in 1849 developed a successful operation for vesico-vaginal fistula. He published his procedure in 1852, and came to New York in 1855. In that year Sims founded the Woman's Hospital, became its Chief Physician, and there carried on the most advanced gynecological work of the day.[47]

Knowledge of antisepsis was completely lacking in Valentine Mott's day and he carried out his extraordinary operations without its aid. Nine years before the Hospital was organized, however, Oliver Wendell Holmes, professor of Anatomy at Harvard Medical School, the father of Oliver Wendell Holmes the famous Associate Justice of the United States Supreme Court, published a significant paper *On the Contagiousness of Puerperal Fever* in which he stated that physicians were unwittingly conveying the disease from patient to patient and insisted that no doctor should attend a woman in childbirth after he had attended a case of puerperal fever or had been present at a post-mortem of one. Although this theory met with opposition, Holmes nevertheless continued to defend it, and in 1855 he published a monograph on *Puerperal Fever as a Private Pestilence* in which he reiterated his views.[48]

It was thus in the dawn of modern medicine that the Jews' Hospital came into existence. It was a day when ethical medicine was gaining ground; when knowledge of disease and public hygiene was advancing; when ether had banished forever operations which of necessity were carried out speedily on struggling patients; when progress was being made in physiology and gynecology; and when the danger of contagion was beginning to be recognized, though not as yet understood.

The first Staff, announced by the Board of Directors on May 21, 1855, included some of the most prominent physicians and surgeons practicing in New York. These men had faith in the efforts of Sampson Simson and his associates.

[46] See footnote 44.
[47] See footnote 44.
[48] See footnote 39.

There were four Consulting Physicians. One was Chandler R. Gilman, a witty conversationalist who in his younger days had supplemented the meagre earnings of his early medical career by writing.[49] He was Professor of Obstetrics and Diseases of Women and Children at the College of Physicians and Surgeons, having been appointed in 1841; and in 1894 he was one of the few contemporary physicians to insist that there was such a thing as criminal insanity and that such criminals should have special treatment. Another was William Detmold, a German, who had introduced orthopedic surgery in New York, had founded an

Fig. 3. Dr. Willard Parker

orthopedic clinic at the College of Physicians and Surgeons in 1841, and was to be the first President of the New York County Medical Association in 1884.[50] William H. Maxwell was the third Consulting Physician, while the fourth was Benjamin W. McCready, a highly respected physician and an early contributor to the funds of the Hospital.

[49] Sketch of the Life and Character of Chandler R. Gilman. J. Munsell. 1866.

[50] Notations from the List of Founders of the New York Academy of Medicine (In possession of the New York Academy of Medicine).

The two Attending Surgeons were Israel Moses, an Army surgeon who also had contributed toward the building of the Hospital, and Alexander B. Mott, the son of Valentine Mott, and his father's assistant during the last sixteen years of the elder Mott's practice. He was an excellent surgeon in his own right, and the founder of the Bellevue Medical College.[51] There were three Consulting Surgeons: the great Valentine Mott; Thomas M. Markoe, one of the founders of the New York Academy of Medicine eight years earlier;[52] and Willard Parker, a leader in surgery, a brilliant lecturer who had taught at Berkshire County Medical College and the College of Physicians and Surgeons,[53] and a co-founder with Daniel Drake of the Cincinnati Medical College in 1835.[54] The Resident and Attending Physician was Mark Blumenthal. A member of the Portuguese Congregation, Mark Blumenthal was its official doctor in its help of the sick poor, family physician to at least half the Congregation,[55] and a respected citizen who lived to be ninety years old.[56] His letter of appointment reads:

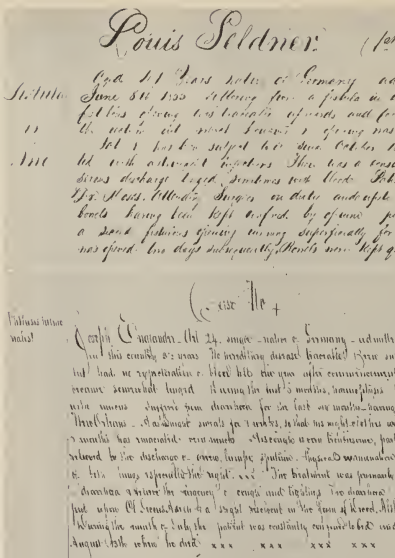
"At a meeting of the Directors held on Monday the 21st Inst., you were unanimously elected Resident Physician to this Institution, & (this is) to apprise you that the Hospital will be opened for the reception of patients daily." The letter was signed by Theodore J. Seixas, Secretary. Dr. Blumenthal was paid two hundred and fifty dollars for his first year's service, and in the following years he received five hundred dollars.

The Hospital doors were thrown open for the reception of patients on June 5, 1855 and a record of the first case was entered in the case book by Dr. Blumenthal on June 8. The patient was Louis Seldner upon whom Dr. Moses operated successfully for a fistula. During the remainder of that year, from June through December, 110 patients were admitted. The Hospital's full capacity was forty-five. (Mount Sinai, the descendent of the Jews' Hospital, has a bed capacity of 856.)

During the first year of hospital service, more precisely on February 11, a ruling was laid down which provided that "patients afflicted with malignant, contagious or incurable diseases" should not be admitted to the Hospital. Tuberculosis was considered incurable, typhoid and typhus were classed as contagious. From December of 1855 through December of 1856, 216 patients were admitted. Only sixteen were asked to contribute to their support under the ruling, "No patient having the ability to pay shall receive the benefit of the Society without charge."

The expenses of the Hospital during its first year of activity offer interesting figures when compared with those of the Mount Sinai of today. The Finance Committee of the Jews' Hospital reported in 1857 that the total expenses for the

[51] See footnote 38.
[52] See footnote 50.
[53] See footnote 50.
[54] See footnote 39.
[55] Interview with Capt. N. Taylor Phillips, son of Isaac Phillips, June 15, 1938.
[56] Meyer, Alfred: Recollections of Old Mount Sinai Days. J. Mount Sinai Hosp., Vol. 3, No. 6, 1937.



Louis Seldner (1st Case.

Sept 11th 1855 Aged 11 Years native of Germany admitted to Hospital June 8th 1855 suffering from a febrile attack in June on examination a fold of skin of the lobule of the left ear, and forwards extending beneath the ramus of the jaw was observable.

11 " Left side of neck also found swollen and glandular.

Sept 1 has been subject to fever since October 1854 and has been ill with abscesses & ulcerations. There was a considerable purulent discharge from the ear. Sometimes both. Patient was operated on by Drs Hays, Metzler, Surgeons on duty and up to this date June 8th the bowels having been kept confined by opium powders formally a dose sufficient generally during superficially for the pain & he was given two doses subsequently & bowels were kept quiet four days by opium

(Case No 4

Baltimore native

Caroline Chamberlain Aet 24. single - native of Germany - admitted June 11th 1855. Affection for this casualty 5 years. The intestine disease has called upon during seven years but had no representation of blood till the year after commencement of cough which has lasted nearly seven months, hemoptysis has been frequent, and much with numerous sweats from shoulders, for the last six months having been for the last 12 months in Baltimore. She almost avoids for drinks, as she might otherwise have continued work and during 3 months has emaciated very much. Abdomen is very tumorous, protuberant at night, and only relieved by the discharge of some liquid feculent. Tongue is unusually clean, and exhibits tuberculous & ulcerous appearance. Pulse 120 to 130 throughout. The treatment was primarily directed to correct the continual diarrhoea & relieve the tenesmus & cough and vomiting. Two diarrhoea was corrected but the patient was just when Dr Strauss left & a hospital assistant on the 4th of Nov. Although the tenesmus & vomiting the patient was constantly confined to bed and grew gradually worse till August 15th when she died. xxx xxx xxx xxx xxx xxx xxx

Died. D. Shadell M.D. Attending Physician. M. Plummer M.D. Attending Physician.

(Case 8th.

Native of Germany aet 20. admitted June 26th 1855. Suffering from rheumatic pains in the knees for about four weeks which stopt him work and alternately ill as affected. Pulse 80 some debility has since not much complained of but for several weeks exacerbations observed a swollen and painful state of the ankle joints with slight pain under the tarsus slightly evaded, and limits occupation. Ordered Tonic Mixture.

June 29th Same symptoms much complained, no pain in the ankles, pulse reduced, and tongue clean. Same medicine and prescription continued.

June 30 complains of pain in his back & loins pain more in 24 hours, pulse irregular and intermitting, skin not unusually hot, urine thick & somewhat increased in quantity. Ordered Hydrochloric effervescent draught

Draught taken & to be repeated until but the motion of the heart is still intermitting and irregular. Heard murmur distinctly heard at the apex of the heart accompanying first sound. Died at 8 P.M. discharged. Found at Rheumatism, but the valvular trouble continued

Dr Plummer. All Physician. D. Shadell. Attending Physician.

FIG. 4. Early case histories

year 1855–56 had amounted to a little over $5,493. The items included in the account are worth examining:

Provisions	$1,726.87
Medicines and Surgical Instruments	447.61
Salaries and Wages	1,511.14
Fuel	297.10
Stationery	33.36
General Expenses, Croton Water, Gas, Assessments, Repairs	1,049.50
Clothing for Patients, Beds and Bedding	429.18
	$5,493.76

Mount Sinai's total expenses for 1938 were over $2,329,000.

In contrast with $447.61 spent by the Jews' Hospital on medicines and surgical instruments, the modern Mount Sinai spent over $200,000 in 1938—almost forty times the entire amount the little institution on Twenty-eighth Street spent in a year! Today medical supplies include items not dreamed of in the Hospital work of the 1850's—for example, supplies for x-ray and electrocardiographic work.

Other portions of that early financial report show similar contrasts. In 1855–56 a little over $1,500 was spent on salaries and wages, while salaries and wages in 1938 came to more than $1,250,000, constituting over half of the modern Mount Sinai's total expenses. Provisions (food) cost the Jews' Hospital approximately $1,726; today Mount Sinai spends over $375,000 annually for food. In 1857 the Finance Committee took pains to explain that although the fuel bill amounted to only $297.10, there had been on hand $200 worth of coal, so that the actual total cost was raised to $497.10 for that year. To feed the boilers which generate steam for heating, cooking, sterilization of instruments, and providing power at the modern Mount Sinai, over $75,000 was spent for oil in 1938.

Of great significance is the fact that included in the sum expended by Mount Sinai in 1938 are items which are conspicuously absent from the brief statement of 1855–56: the School of Nursing, the Social Service Department, the Out-Patient Department, the Laboratories, research, and post-graduate medical education. These branches of hospital work did not exist in the days when the Jews' Hospital first opened its doors. Their gradual inclusion in later reports forms a series of milestones marking the progress of medicine and of hospital administration.

The rule concerning patients afflicted with incurable diseases was apparently not rigidly adhered to, according to the following statement in the report for 1856:

"Several whose diseases were known to be incurable, were nevertheless admitted, because, in the opinion of the physicians and surgeons, they were susceptible of relief, and because, in the opinion of your Committee, consumptive patients should not be permitted to linger out a wretched existence in a strange asylum, whilst a Jews' Hospital is in being to afford hope to the dying pilgrim."

The steady flow of European immigration into the United States and the conditions in which many of these immigrants lived, conditions which were increasing the percentage of typhoid and tuberculosis patients, are reflected in this early report. Of the two hundred and sixteen patients admitted, only five were natives of the United States, the largest number, one hundred and ten, coming from Germany. Of the fourteen deaths which occurred at the Hospital that year, half were caused by typhoid and tuberculosis.

The minutes of the Board of Directors' meetings indicate that in October, 1856, the Directors had become disturbed over the number of typhoid cases which were refused admission to the Hospital because the disease was considered contagious. They turned to the Medical Board to ask once again if its contagious character was definite. The answer was in the affirmative, but a significant resolution was sent to the Directors:

"Resolved, that the simple fact of a disease being contagious should not preclude its reception into an Hospital, and that proper regard to separation, ventilation and the number admitted to the ward, will obviate to a great extent any danger from the reception of patients suffering under typhoid fever."

The Board of Directors then instructed the Executive Committee to admit such cases at its discretion. Nevertheless, the report for 1856 contains a strong plea from the Visiting Committee that rather than reject typhoid patients, some plan should be devised for a separate building to accommodate them. This appeal is characteristic, not only of the contemporary layman's theories about medicine, but also of the spirit that animated the Hospital's founders.

"Your Committee cannot refrain from calling the serious attention of the Board of Directors to a renewed consideration of the subject of admitting typhoid fever patients. Every week their feelings are harrowed by listening to tales of woe they cannot ameliorate, by appeals from the most abject heirs of sickness, poverty and want, to whom they must refuse admittance because they are laboring under typhoid fever, and through fear that its contagious character might infect other patients.

"Can no plan be devised to erect a building where they might be nursed and tended? Are those poor creatures to have no chance of recovery? Must they perish or be sent from your doors to enter other hospitals? Think what a sad disappointment it is to them to be rejected by their brethren in faith.

"The Committee are aware that you have asked the Faculty whether typhoid fever is contagious, and that the answer was in the affirmative. But will that alleviate the distresses of those who appeal to you for admission? Renew again the consideration of this subject, and, if necessary, appeal to the Jewish community for aid in this emergency. Such an appeal to Israel has ever been successful. . . . "

The next installment will deal with the Hospital's early participation in a national emergency during the Civil War; with the state of hospital nursing in that period; with the public attitude toward post-mortem examinations; and with some of the striking figures added to the original medical staff.

Julius Wolff

December 3, 1870—January 26, 1942

Dr. Julius Wolff died suddenly of a heart attack at his desk while preparing notes for a First Aid course he was conducting. At 72, he was young in mind, in full possession of his great skill, and zealous in discharging his duties to his family, to his patients, and to the war effort.

He received his preliminary education at the Sachs Collegiate Institute, graduated from Harvard in 1890, and three years later received his Doctor's degree from the College of Physicians and Surgeons, Columbia University. For two years he interned at the German, now Lenox Hill, Hospital, and then continued post-graduate studies at Strasbourg, Cologne, Paris, and London.

During his first three years in practice, in addition to his work in ophthalmology, he devoted much time to surgery of the ear, nose and throat. His first appointment in his chosen field was that of Ophthalmologist at Randall Island Hospital and in that capacity he served until 1905. Two years later he came to The Mount Sinai Hospital as an Assistant Adjunct Attending Ophthalmologist and in 1915 he was placed in charge of the Eye Clinic. He was rewarded for the excellence of his work when in 1923 he was raised to the rank of Ophthalmic Surgeon to the Hospital and entrusted with the Department of Ophthalmology.

In the nine years during which he led and trained members of that department, he left an indelible mark by his uniformly great surgical skill, by his conservative and sound clinical judgment, and above all, by helping the younger men unstintingly and graciously.

He retired from active Hospital service in 1932 and was promptly appointed Consulting Ophthalmic Surgeon to the Hospital.

He was a member of the American Medical Association, the American College of Surgeons, the American Academy of Ophthalmology, the New York State and County Medical Societies, and a fellow of the New York Academy of Medicine.

Dr. Wolff, in addition to his success in medicine, achieved a balanced life with his home, golf, music, and later wood-carving, all contributed to a wholesome unity. No one came in contact with him without feeling the warmth of his personality and without being impressed by his tolerance of view and his kindness of heart. His love of humanity was reflected in his social concepts and in his personal relations with his colleagues. He was respected by all and was loved by those who knew him well.

Henry Minsky

Philip Finkle
November 2, 1894—March 12, 1942

Philip Finkle was born in Hartford, Connecticut on November 2, 1894. He was the oldest of five children of a successful merchant. However, when Philip entered high school, financial reverses incident to the depression of 1907 unsettled the comfortable life of the family who had at that time moved to New York. He attended the Boys High School in Brooklyn and soon came in contact with the more unpleasant aspects of life. Cold, uncomfortable living quarters on the lower east side, an hour's walk to school in the early morning, and not so rarely to bed without a warm supper—these were the experiences of his adolescence. They left their mark, they shaped his social consciousness and made him an uncompromising foe of the economic injustices of modern life and an enthusiastic believer in a better world order to come.

Outside difficulties, however, could not suppress his urge for knowledge nor did they interfere with the development of his great talents. He was graduated at the top of his class and entered Columbia College where he received an A.B. degree in 1916. He completed his medical studies during the first World War and obtained his M.D. degree in 1918. He interned at The Mount Sinai Hospital in New York and after completion of his internship served as admitting physician for two years. He often referred to this assignment as the most valuable period of his training. Here he utilized the experiences he had gained during his school and hospital years and here he developed his unusual analytic abilities which made him the excellent diagnostician of later years.

After this thorough preparation he did not choose to settle down and develop a lucrative practice to which his ability and knowledge would have entitled him in those years of apparently expanding prosperity. His aim was higher, he searched for the fundamentals in the art and science of medicine and thus he entered upon a career of investigation. He spent one year in San Francisco with Gilbert Lewis, one year with A. V. Hill in London, and one year with Meyerhof in Kiel and Berlin. He returned to New York inspired by the association with these great scientists and ready to embark upon original investigations. He joined the Hospital of the Rockefeller Institute as assistant resident physician. There he became associated with Avery in a study of the metabolism of pneumococci, a problem which he pursued for several years. In 1926 he returned to The Mount Sinai Hospital where he joined the reorganized laboratories. For nearly two years he worked in the department of morbid anatomy. Following an illness of several months due to an infection acquired in the post-mortem room he resigned from the department and resumed his investigations of the metabolism of bacteria. Several publications were the fruit of his labor. He engaged in research on vitamin C, especially its quantitative determination in various diseases.

Laboratory research, however, did not satisfy his ambition because fundamentally he was a clinician. In 1929 he was appointed adjunct in medicine at

The Mount Sinai Hospital. Among his various assignments outside of the routine duties on the wards, was the Arthritis Clinic; in later years he was engaged in the supervision of the therapy of pneumonia patients on the First Medical Service of the hospital. Through all these years he continued to work in the little laboratory on top of the north wing of the administration building.

Finkle was a not a prolific writer but everyone of his publications bore the stamp of painstaking, critical investigation and of an original mind. As a physician he was an excellent diagnostician. Finding recognition outside of The Mount Sinai Hospital he was appointed associate visiting physician at Harlem Hospital in 1934. Although medicine was dominant, his interests were wide. His knowledge of literature and fine arts was great, but above all he was deeply concerned with problems of philosophy and economics. He realized the ills of the world situation a long time before they became as evident as they are today. His was a deep love for humanity and a sincerity of belief which made him appear hypercritical of the weakness and failings of others. Philip Finkle was no opportunist. He stood by his convictions and was frank in their expression. He did not deviate from his chosen path to make friends; he was sometimes harsh in his judgment. But those who knew him well, knew his sensitivity, his kindness, and his loyalty.

Paul Klemperer

ABSTRACTS

Authors' Abstracts of Papers Published Elsewhere by Members of the Mount Sinai Hospital Staff

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Vascular Allergy, Pathogenesis of Bronchial Asthma with Recurrent Pulmonary Infiltrations and Eosinophilic Polyserositis. J. Harkavy. Arch. Int. Med. 67: 709, April 1941.

Eight cases, seven of which suffered from typical bronchial asthma and one from bronchospasm and cough, are reported. The exciting factors in two were identified as synergistic sensitization to pollen, foods and bacterial products, while in the remaining six, bacterial allergy due to chronic infection of the sinuses played a dominant rôle.

The major attacks of asthma were associated with the following symptoms: 1) migratory interstitial lesions in the lungs with sputum eosinophilia in six cases; 2) reversible sterile eosinophilic pleural effusions in six cases; 3) peritoneal eosinophilic exudates in three cases; 4) reversible pericardial involvement in one case and irreversible involvement in two cases leading to adhesive pericarditis; 5) reversible electrocardiographic abnormalities fluctuating with the asthmatic seizure involving the T-waves and QRS complexes in four cases and irreversible abnormalities in two cases with a fatal issue; 6) increase in the total white count to a maximum of 40,000 and eosinophilia in the bone marrow and the peripheral circulation to a maximum of 84 per cent; 7) fugitive polyarthritis in three cases; 8) hemorrhagic necrosis in Scarpa's triangle in one case, angio-neurotic edema and purpura in two cases as well as subcutaneous nodules in one case. Biopsies of each of these cutaneous lesions showed perivascular eosinophilic infiltrations, in addition to which the subcutaneous nodule disclosed areas of periarteritis nodosa.

The simultaneous appearance of eosinophiles in the sputum, in serous exudates and in the perivascular infiltrations in the skin lesions progressing to periarteritis nodosa, implied active involvement with increased permeability of the vessels of the lungs, serous membranes and cutaneous tissues, which accompanied the migration of the eosinophiles.

This would suggest that the pulmonary infiltrations, the eosinophilic serous exudates the electrocardiographic changes, all were the result of hyperergic vascular reactions in the respective tissues as mirrored in the skin biopsies. The asthmatic seizures accompanying the pulmonary infiltrations coinciding or alternating with the lesions in other enumerated shock tissues were interpreted as symptomatic expressions of the altered response in the vessels of the lungs and bronchi and but one aspect of a diffuse vascular and mesodermal reaction subject to the same allergenic provocation.

The development of mediastino-pericarditis which resolved completely in one case and which progressed to the state of constrictive pericarditis and subsequently polyserositis in two cases suggested that these syndromes were sequelae of hyperergic perivascular reactions of the serous membranes and myocardium.

The eosinophilia in the perivascular infiltrations in the skin lesions and subcutaneous nodules alongside of blood vessels in various stages of involvement progressing to periarteritis nodosa testifies to the allergic nature of these reactions and supports the view that periarteritis nodosa represents a hyperergic vascular response. The increase in the blood eosinophilia and the total white blood count in the bone marrow indicates that the marrow participated as a shock organ.

The differences between the cases which died and those which survived lay in the increased number and intensity of involvement of the various shock tissues. The latter

determined the development of seemingly unrelated clinical syndromes such as constrictive pericarditis, polyserositis, etc., the allergic nature of which was identified by the asthma and eosinophilia. The interrelationship between the two groups of patients was further accentuated not only by the similarity in the pathogenesis but also by the identity in the biopsy finding of hyperergic vascular involvement which in the fatal case progressed to periarteritis nodosa. Those who survived may be regarded as *formes frustes* or potential types of this disease.

Extraperitoneal Injuries Simulating Intraabdominal Trauma. M. A. Sallick. S. Clin. North America 21: 417, April 1941.

Cases illustrating the frequent occurrence of abdominal manifestations with injuries which are strictly extraperitoneal are presented. Visceral trauma within the abdomen may be closely simulated by the following lesions: abdominal wall contusion, chest injury or rib fractures, retroperitoneal hematoma, fracture of the spine or lumbar transverse processes, urinary tract injury and fractures of the bony pelvis. It has also been seen with severe head trauma. With any of these, the so-called "pseudoperitoneal syndrome" may appear, giving rise to a clinical picture which strikingly imitates the "acute abdomen." Since the methods of treatment of the two are quite distinct, their differentiation is of utmost importance. Points in their differential diagnosis are discussed.

Treatment of Measles With Convalescent Serum and Concentrated Adult Normal Serum. J. L. Kohn, I. F. Klein, and H. Schwarz. J. Pediat. 18: 476, April 1941.

It was confirmed that the intravenous injection of adequate amounts of convalescent serum if given in the preeruptive stage of measles, modifies the course of measles in most cases. However, the intravenous injection of large amounts of convalescent serum during the eruptive stage had very little effect on the subsequent course of measles. When large amounts of concentrated normal adult serum were given during the preeruptive stage, measles was not modified. Empirically the antibody content of this concentrated serum was equal to that of the convalescent serum.

Fate of Spontaneous Mammary Carcinomas in Mice After Simple Biopsy. R. Lewisohn, C. Leuchtenberger, R. Leuchtenberger, and D. Laszlo. Cancer Research, 1: 324, April 1941.

In a previous paper the authors reported complete disappearance of 38 spontaneous breast carcinomas in mice (strain A, Roscoe B. Jackson Memorial Laboratory) following intravenous treatment with spleen or yeast extracts. Biopsies had been performed in every case in order to establish the malignant nature of these tumors beyond doubt. The objection was raised that the successful treatment of these tumors was due to the biopsy and not to the treatment. In order to meet this objection, 81 strain A mice with a high incidence of spontaneous mammary carcinoma were subjected to biopsy and were used as controls. No treatment was given. In none of these animals was a permanent and complete regression of the tumors observed. All control animals are dead, the vast majority with large and many with multiple tumors. Forty-nine per cent of the autopsied controls of strain A presented metastatic carcinomas of the lungs. The authors have never seen a metastatic carcinoma of the lungs among the autopsied healed tumor mice. Temporary regressions in the size of these tumors occur spontaneously. They are not necessarily due to any form of treatment. It can be stated without reservation that a biopsy does not cause disappearance of these tumors.

Gunshot Wound Through the Abdominal Aorta. B. A. Kornblith. Ann. Surg. 113: 657, April 1941.

A 39-year-old white man sustained a gunshot wound of the abdomen with a .22 calibre bullet. The course of the bullet was as follows: the skin at the xyphoid cartilage; rectus abdominis fascia and muscle; parietal peritoneum, the superior surface of the left lobe of the liver, the substance of the left lobe of the liver, gastrohepatic ligament, the lesser sac,

transverse mesocolon superior border of the transverse portion of the duodenum; through the abdominal aorta into the body of the second lumbar vertebra. No hollow viscus was perforated in transit and there was no bleeding from the aorta proper. The patient died of bronchopneumonia on the ninth postoperative day. The stellate wounds in the aorta were discovered post mortem.

Adrenal Cortex in its Relation to Virilism. N. Mintz and S. H. Geist. Endocrinology 1: 316, April 1941.

The authors have collected a series of 10 cases of the adrenocortical syndrome in women, 6 of them caused by carcinoma of the adrenal cortex, 2 caused by adenoma of the adrenal cortex, 1 case of massive intra-adrenal hemorrhage, and 1 case caused apparently by a lesion of the pituitary gland. It is now believed that the vast majority of such cases are caused by adrenal cortical lesions, such as carcinoma, adenoma, or hyperplasia. According to the work of Broster and Vines and Grollman, one must look to the embryology of the adrenal for their pathogenesis. Although these findings have not been universally confirmed, this is a fruitful field for further research. The endocrine investigation has uncovered the information that some of the cortical carcinomas produce a considerable quantity of male sex hormone. In addition Butler and Marrian believe that they have isolated an entirely new steroid which is specific for this condition.

Clinically, these patients present a picture of defeminization and masculinization, the severity depending on the extent of the lesion and the age of the patient. The treatment consists of unilateral adrenalectomy or partial adrenal resection, depending on the nature of the lesion. The prognosis is only fair inasmuch as the opposite adrenal is often atrophic.

Effect of Edema and Integumentary Infiltrations on Basal Metabolism, Electrocardiogram and Blood Cholesterol. E. Moschcowitz. Arch. Int. Med. 67: 828, April 1941.

None of the previously considered hypotheses for the explanation of the lowered basal metabolism in "nephrosis" is adequate. Evidence is adduced to prove that it is due to the edema fluid which acts as a suit of clothes, preventing conduction, radiation and convection of heat. This mechanism of the lowered metabolism applies not only to "nephrosis" but to other conditions accompanied by edema or integumentary thickenings. I refer especially to myxedema, the edematous form of scleroderma and to the edema of chronic right-sided cardiac failure unassociated with dyspnea and ichthyosis. Concomitant findings in these conditions associated with a lowered basal metabolism are a low electrocardiographic curve indistinguishable from that of the myxedema heart and a high level of cholesterol in the blood. Finally, these conditions are characterized by an unusual tolerance for the administration of thyroid preparations.

Results of Plastic Operations on the Renal Pelvis and Ureter. A. Hyman, and S. F. Wilhelm. Surg. Gynec. & Obst. 72: 764, April 1941.

The results of 32 plastic operations on the renal pelvis and ureter, done at The Mount Sinai and Beth Israel Hospitals, have been reported and analyzed. Relief of obstruction was the primary object of the surgical treatment of hydronephrosis. In some cases, the dilated pelvis was also resected or plicated. The various types of plastic operations employed are discussed and evaluated, and illustrative cases are recorded in some detail. Direct pyeloscopy through the nephrostomy sinus was done in 2 cases. In 1 instance, patency of the anastomotic stoma was reëstablished, following electrocoagulation of a valve-like mucosal fold. The authors believe that side-to-side anastomosis of the ureter and pelvis, when feasible, is preferable to section and re-implantation.

SERUM PROTEINS IN HEALTH AND DISEASE[1]

JOHN P. PETERS, M.D.

[*Professor of Medicine, Yale University School of Medicine, New Haven, Conn.*]

Bright, his associates and immediate followers recognized that the serum of some patients with granular kidneys was deficient in protein. When, therefore, Starling propounded his explanation, reinforced by experiment, of the exchange of fluid between the blood stream and the tissues, all the facts needed to elucidate the cause of renal edema were at hand. By this time, however, the import of Bright's discovery had been largely lost, owing to his use of the term "thinning of the blood." Bright rightly attributed the depletion of serum protein to loss of albumin in the urine; but, in the next generation the impression grew that it was evidence of hydremia, the accumulation of excessive water in the blood, as if the latter shared in the edema of the tissues. Oddly enough Bright was even frequently cited as the authority for this view. Dr. Albert Epstein (1, 2) recognized the true significance of Bright's discovery, its logical connection with Starling's theory and its bearing upon the origin and treatment of nephritic edema. By experiment he confirmed and extended Bright's observations and demonstrated their implications. It is, therefore, a signal honor to be invited to speak on the subject of the serum proteins in health and disease in the place where their significance to clinical medicine was first truly appreciated and proclaimed.

It is not my intention to dwell long on the particular aspect of the problem that Dr. Epstein emphasized; this would be bringing coals to Newcastle. Nor can I hope in the brief time at my disposal to review all the variations of the serum proteins in disease. I shall merely touch in passing upon the function of the proteins in facilitating the exchange of fluids, devoting the major part of my attention to the examination of more remote implications of the Starling theory and certain functions of the proteins that are generally neglected. With your indulgence I shall venture upon some speculations which, I hope, will not seem to you altogether idle.

The capillary walls are normally impervious to proteins, although they permit the free passage, by diffusion, of salts, sugar, nonprotein nitrogenous compounds and other solutes of moderate molecular size. Fluid in the extracellular tissue spaces about the capillaries contains only minute amounts of protein. The protein within the capillaries, therefore, exerts an osmotic pressure which would tend to draw water continuously from the extracellular spaces into the blood stream, were it not opposed by the capillary blood pressure. Figure 1 depicts U-tubes with membranes across the connecting arms which are permeable to water, but not to protein. In *A* protein has been introduced into the left arm of the tube. Immediately water flows from the right arm to the left until the

[1] Presented as part of the celebration of the Ninetieth Anniversary of The Mount Sinai Hospital, Symposium on Blood Chemistry, March 6, 1942.

height of the column of water in the left arm exceeds that in the right by an amount which is equal to the osmotic pressure of the protein which, in turn, is proportional to the concentration of the protein. This state is depicted in *B*. If, now, a piston is inserted into the left arm, the fluid will be restored to its original level when the pressure exerted on this piston equals the osmotic pressure of the protein, the condition shown in *C*. The membrane, in this case, represents the capillary wall, the left arm is the capillary blood stream, the right arm the extracellular tissue spaces, the piston the blood pressure created by the contractions of the heart.

Figure 2 represents schematically the capillaries, with blood flowing from left to right. The vertical arrows pointing upward above the vessels stand for the blood pressure, which diminishes steadily from the arterial to the venous end of the capillary. The arrows pointing downward represent the osmotic pressure

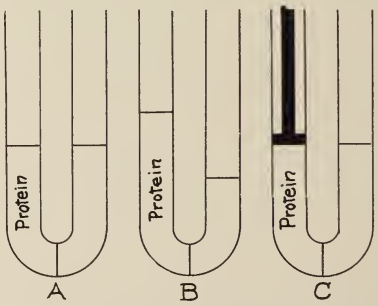


FIG. 1. A schematic diagram of the principles of the Starling theory

of the proteins. The blood pressure tends to drive fluid out of, the protein osmotic pressure to draw it into, the capillary. The movement of fluid, therefore, will depend upon the difference between the lengths of the two sets of vertical arrows, which is indicated by the diagonal arrows below the vessels. Ordinarily, as in *A*, the blood pressure predominates at the arterial, the protein osmotic pressure at the venous, end of the capillary. The result is a more or less balanced circulation of fluid, escaping at the arterial end and returning at the venous end of the capillary. When the concentration of protein in the serum falls, as in *B*, the return flow diminishes; consequently fluid is discharged into the extracellular spaces faster than it returns and edema ultimately results. Increase of capillary pressure by reason of venous stasis—for example, in heart disease—will have a similar effect, illustrated in *C*.

It must be recognized that capillary and arterial blood pressure are not directly related to one another; in fact, arteriolar constriction, though it raises the arterial blood pressure, by retarding blood flow reduces the pressure in the cap-

illaries. On the other hand, capillary pressure is greatly influenced by venous pressure, since this causes blood to back up into the capillaries. Under no circumstances does the osmotic pressure of the serum proteins alone determine the direction of motion of fluids between the blood stream and the surrounding tissue spaces. Always this motion is governed by the resultant of protein osmotic pressure and the capillary blood pressure. It follows that a moderate reduction of serum albumin may determine the appearance of edema if the capillary blood pressure is, for any reason, increased. Conversely, if serum albumin is low, only a moderate increase of capillary pressure will be required to produce edema. In clinical practice it is such conjoined forces that are usually responsible for

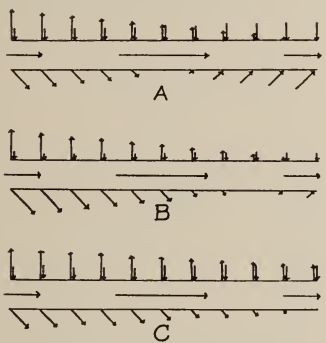


FIG. 2. Diagrammatic representation of the transfer of fluid between capillaries and interstitial spaces of the body. The horizontal parallel lines represent capillaries with blood flowing from left to right. The vertical arrows above the capillaries represent the capillary blood pressure, pointing upward, the colloid osmotic pressure pointing downward. The diagonal lines below the vessels indicate the direction of motion of fluid to and from the capillaries, which is determined by the difference between the height of the two sets of vertical arrows. *A* represents conditions in the normal animal; *B* in nephrosis or malnutrition, when serum albumin is reduced; *C* in heart failure, venous stasis and other conditions in which the capillary blood pressure is increased.

edema and it is on this account impossible to fix definite protein concentrations at which edema is likely to appear. Edema in patients with heart failure, for example, may prove unduly intractable if, as the result of malnutrition, the serum proteins are even slightly reduced. Both experimental and clinical evidence indicates that in cirrhosis of the liver ascites is unlikely to occur until the osmotic pressure of the proteins in the serum falls below normal. Only a slight reduction of protein osmotic pressure is required to induce edema in patients with anemia.

Because of its smaller molecular size and other properties, as yet not entirely understood, the albumin fraction of the serum proteins exerts a far greater osmotic pressure than globulin does. It is, therefore, the albumin which is important

in the analysis of edema, and no determination of proteins that does not include separate measurement of these two large fractions is satisfactory. In all other respects, also, including its origin and functions, albumin appears to be so distinct from the globulins that they should be considered as independent variables. If this is true the expression A:G ratio, so commonly used, has no significance and can lead only to confusion.

Serum albumin may be depleted, not only by leakage into the urine or by plasmapheresis, but by a deficiency of protein in the diet. It therefore serves as a measure of malnutrition or protein starvation. On the other hand, globulin is little affected by any of these disorders. In fact, since globulin is increased by most infections and a variety of non-infectious diseases and disorders, it is often elevated in conditions attended by malnutrition. Reduction of serum albumin

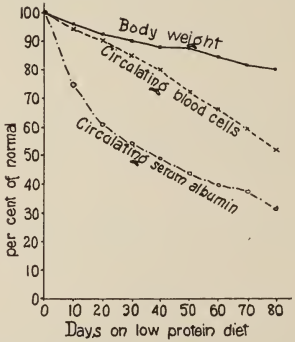


FIG. 3. The relative loss of body weight, serum albumin and circulating blood cells of a dog receiving a protein-free diet. From Weech, Wollstein and Goettsch (3).

is important, not only for its own sake and because it gives rise to edema, but as an indication of more serious losses of protein from other sources. Figure 3, from data of Weech (3) dealing with a dog maintained for 80 days on a diet containing minimal amounts of protein, gives an idea of the relative magnitude of these losses. From this figure it may be seen that, as serum albumin falls, the number of red blood cells and the hemoglobin also diminish and body weight declines steadily even after edema has appeared. This figure does not, however, give an accurate impression of the distribution of the protein deficiency among the different tissues of the body. A 70 per cent reduction of albumin sounds greater than a 50 per cent reduction of hemoglobin; but since there is 4 times as much hemoglobin as there is albumin in blood, the actual loss of hemoglobin is almost 3 times as great as the loss of albumin. The actual state of the animal at the end of this 80 days is represented in Figure 4. Of the total protein lost, almost 80 per cent came from the tissues, only about 3 per cent from the serum

proteins, the remainder from hemoglobin. A moderate deficiency of serum albumin, then, may denote a severe depletion of tissue protein. If this were more generally appreciated, there would be less surprise that in malnutrition serum albumin cannot be restored with great celerity.

There are some indications that during recovery from malnutrition the reconstruction of serum albumin may wait upon the reconstruction of more important tissue proteins. It seems to be impossible to increase the weight of malnourished animals by diets high in carbohydrate and fat, but in which protein is deficient either in quantity or quality. Lack of protein appears to interfere with the proper utilization of other foodstuffs, although the manner in which it interferes is not clear. If the protein deficiency arises merely from deprivation of protein it can be rectified by the administration of protein. If serum albumin is depleted

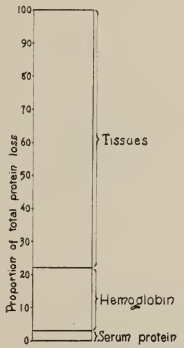


FIG. 4. The source of the proteins lost by a dog in the course of 80 days' subsistence on a protein-free diet. From Weech, Wollstein and Goettsch (3).

by direct drainage (by albuminuria or by plasmapheresis) it seems to be more difficult to restore it by feeding alone. In this case reconstruction of serum albumin is presumably limited, not only by lack of protein, but also by the specific capacity of the animal to manufacture serum albumin. This it is that makes treatment of the nephrotic syndrome with high protein diets so discouraging. Even if appetite and digestion are equal to the task—and they are too often capricious, to say the least—the returns in serum albumin are woefully slow and small. Nevertheless, studies of nitrogen metabolism have proved that when patients with the nephrotic syndrome eat enough protein, they assimilate it and store it.

Some years ago Grabfield (4) reported certain peculiarities in the sulfur metabolism of patients with the nephrotic syndrome. Alving (5) subsequently found that serum albumin in this condition contains less than the usual quantity of cystine. Goettsch and Reeves (6) have discovered that when hypoproteinemia

becomes extreme a fraction of serum albumin loses its antigenic properties. Finally it has been shown that a fraction can no longer be crystallized. Taken together, these observations suggest that, when the drain on serum albumin becomes extreme, the body is forced, in its haste, to turn out an incomplete and probably inadequate protein. It is necessary to point out that these abnormalities are not detected by the usual precipitation techniques; they do not demonstrably alter the general physical properties of the proteins.

Measurement of the concentration of albumin in the serum does not necessarily give an accurate impression of the quantity of albumin in the circulation, because a three-dimensional function can not be evaluated by two-dimensional measurements. The actual quantity of albumin in the circulating blood can only be obtained by multiplying the concentration of albumin in the serum by

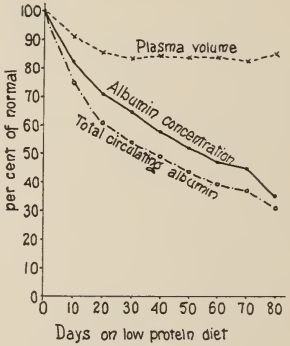


FIG. 5. The effect of a protein-free diet upon the plasma albumin and plasma volume of a dog. From Weech, Wollstein and Goettsch (3).

the volume of serum. Dehydration with hemoconcentration may mask an albumin deficiency completely. Starling's theory demands that, unless there is a compensatory reduction of capillary blood pressure, every reduction of serum albumin must provoke a certain degree of hemoconcentration. Published data from clinical and experimental material frequently have not been consistent with this postulate. There is, as I shall hope to show, some danger in accepting these data without critical scrutiny of the procedures employed to measure serum volume. Weech (3), in carefully controlled experiments on dogs, found that serum albumin begins to fall as soon as protein is withdrawn from the diet. As it diminishes, fluid tends to escape more rapidly from the capillaries, causing the blood volume to contract. In Figure 5, from data of one of these experiments, the top line represents the plasma volume, the middle line the concentration of albumin in the serum, the bottom line the total circulating albumin, the product of volume and concentration. It will be seen that after 20 days, because of the reduction

of plasma volume, the total circulating albumin has diminished 40 per cent, the concentration only 30 per cent.

The proteins are not the only substances that are restrained by capillary membranes. Lipoids are similarly restrained (7). Unlike the proteins, however, they exert a negligible osmotic pressure because of their relative insolubility and also because they are largely or entirely held in solution by adsorption to the proteins. Many other substances are similarly carried by the proteins, being held either by adsorption or by chemical combination. In fact this faculty of carrying other substances, which Bennhold (8) terms the "vehicular power", is one of the most important properties of the proteins and the one to which I want to devote most of the remainder of my time. Upon this property depend most of the functional tests that involve the selective excretion of injected dyes or the measurement of fluid compartments by means of such dyes. The capillary walls are permeable to some—if not most—of these dyes. These should, therefore, escape at random into the extracellular fluids were they not attached to the proteins.

The statement that the intact capillary walls are impervious to protein and lipoids must be qualified. Slight local leakage which may result from vasomotor disturbances or minute vascular defects may be neglected. The possibility must and obviously does exist that proteins or the materials that they carry must be able to escape from the blood stream in a less accidental manner when they are needed by the tissues. Lipoids, for example, must be able to find their way to the tissue cells. When Man (7) produced hemoconcentration in human subjects by having them remain motionless in the standing position, lipoids and proteins usually varied proportionately; but occasionally there was an independent deviation of one of the lipoid components that could only be ascribed to the sudden removal from or addition to the blood stream of a certain quantity of this substance. It can no longer surprise us that large molecules can be moved across membranes in response to metabolic needs and in conjunction with metabolic activities. Such phenomena, however, should probably be regarded not as passive transfers governed by the ordinary laws of membrane equilibrium, but as processes that involve chemical reactions and require the expenditure of energy. It is, therefore, proper, in considering the behavior of the vascular membranes as barriers, to speak of them as impervious to proteins and lipoids, in much the same sense that the membrane of the red blood cell is regarded as impervious to sodium, potassium, phosphate and other ions.

It is reasonable to suppose that lipoids and other compounds that are carried by the proteins can be removed from the blood stream through intact capillary walls throughout the circulatory system, else there is no conceivable way by which the cells of the tissues could be supplied with these essential materials. Certain adsorbed solutes, like the dyes, seem to be selectively abstracted by particular tissues, such as the liver and kidneys. That proteins are treated in the same manner is likely, but less certain, although there can be no doubt that they do escape from the circulating blood. Whipple and his associates (9) have shown that if blood serum is injected into the veins of a normal dog, the concen-

tration and the total quantity of protein in the circulation are increased for only a short time. Evidently the injected protein is rapidly withdrawn from the blood stream. Furthermore, it can apparently be ulitized by the tissues, because its injection does not increase the urinary excretion of nitrogen. This is the most direct evidence that serum proteins are not mere mechanical aids in the exchange of water and the transportation of solutes, but that they may also serve a nutritive function.

It is reasonably well established that serum proteins cross capillary membranes with relative freedom in special parts of the circulation. When Starling first proposed his theory he recognized that its application to the portal system, especially in the liver, presented difficulties. In the portal capillaries the blood pressure is altogether too low to balance the osmotic pressure of the plasma proteins. If, then, no especial provision were made in this part of the circulation, the extracellular fluid of the liver and other tissues in the portal system would be sucked dry. Starling, therefore, suggested, with the support of some experiments, that the fluid in the extracellular spaces of the liver must contain protein in relatively high concentration. This prediction has been verified by several observers, most recently by McCarrell, Thayer and Drinker (10). They have found that the concentration of protein in lymph from the liver is practically the same as that in the blood serum. This naturally raises the question whether the extravascular protein originates *in situ* or whether the walls of the capillaries in these regions are more permeable than those of the systemic circulation in general. That some of the protein originates *in situ* cannot be denied. In fact, Whipple, (11) and others concede to the liver the main rôle in the manufacture of the serum proteins. There is, however, cogent reason to believe that the capillaries of these regions are also unusually permeable.

Drinker (12) has shown that foreign proteins, injected into the blood stream, rapidly find their way into the lymph of the thoracic duct. Even before this, however, Smith (13) proved that brilliant vital red, when injected into the blood stream, appears in the lymph of the thoracic duct system in high concentration within 5 minutes. If this dye is held in the blood stream by adsorption upon the proteins, as Gregerson (14) believes, it may be inferred that it escapes from the vessels with the proteins to which it is attached. Be that as it may, its escape from any part of the circulation denotes that the capillaries of this region are unusually permeable. The blue dye, T 1824, discovered by Evans and recently popularized by Gregerson (15), differs no whit in its behavior from brilliant vital red. It remains an enigma that, in the face of this evidence, Whipple should have elected to use the dye blood volume method instead of the carbon monoxide method; and that he should, even in his last papers about radioactive iron (16), speak of the blood volume dyes as the most accurate means of measuring the volume of the circulating plasma. Elegant refinements of techniques for measuring the concentration of these dyes and mathematical formulae for extrapolation along disappearance curves can do nothing to overcome this fundamental defect in dye blood volume methods. At best they measure the volume of the circulating blood plasma plus an indeterminate portion

of the thoracic lymph system. It is not surprising, then, that blood volumes measured by these procedures regularly exceed, by an average of 10 per cent, volumes measured by methods that depend upon the labelling of blood cells. Even for the measurement of changes of plasma volume in response to physiologic and pathologic disturbances dye techniques are of no value unless it can be assumed that the volume and flow of lymph in the system drained by the thoracic duct remain unchanged, an assumption that is altogether at variance with what little we know of this system (17, 18, 19). The most extreme example of the unreliability of the blue dye method is found in Freeman's (20) experiments on surgical shock. Although, by every other criterion, the blood in this condition became inspissated, according to the blue dye method the plasma volume appeared to expand enormously. The anomaly was explained after the dogs died or were sacrificed, when all the upper abdominal organs were found to be deeply stained with the dye.

To lay so much emphasis on this point in a discussion of the serum proteins may seem irrelevant. It is, however, peculiarly pertinent for two reasons. First, certain inferences that have been drawn from studies of the plasma volume, if they were accepted, would threaten the Starling theory. The Starling theory is, however, based on sound thermodynamic principles, while the dye methods are no stronger than their empirical background.

These experiments have, however, other important implications. If the blood volume dyes are retained in the circulation by attachment to the proteins or can escape only when the vessels become permeable to the proteins, these dyes may be used to trace the movements of the serum proteins. Drinker (13) in his original monograph on the lymph and lymphatics, proposed that lymph is identical with extracellular fluid. If this were the case, it would have to be presumed that the capillaries of the peripheral circulation were relatively permeable to proteins. It would follow that dye blood volume methods must be even more unreliable than they have proved, because an unpredictable proportion of dye would be constantly leaking from the circulation at every point. In commenting on Drinker's hypothesis in another connection, I suggested that the lymphatics have the capacity to remove from the extracellular spaces proteins and other particulate matter which is excluded from returning to the blood stream; and that the accumulation of such material in the lymphatics, by exerting a colloid osmotic pressure in these vessels, can provide the force required to fill them and to establish a lymph-flow. When Dr. John Homans was in New Haven I had the opportunity, with Dr. Alexander Winkler, to study 2 patients with massive lymph-edema of the lower extremities. The fluid which accumulates in the legs of such persons, according to Drinker's analyses and our own, contains about 4 per cent of protein. This, Iverson and Johansen (21) have estimated, is the highest concentration that proteins can reach in pericapillary fluids, if the Starling theory is sound. If there was slight, but gradual, seepage from the capillaries of protein that was precluded from returning to the circulation because the normal lymphatic route was obstructed, the concentration of protein in the extracellular fluids would rise to just this point, because reab-

sorption of fluid by the osmotic pressure of the serum proteins would cease when the concentration of protein in the extracellular fluid reached about 4 per cent. If, on the other hand, the blood capillaries were so permeable that they allowed 50 per cent of the serum protein to escape, dyes would measure, not only the volume of the circulating plasma, but also half the volume of the extracellular fluids, and the concentration of dye would be half as high in the lymph-edema as it was in the blood serum. Actually, after intravenous injections of brilliant vital red, none of the dye could be detected in the edema fluid. When these same patients are suspended so that the fluid can seep under the force of gravity into the lumbar region where the lymphatics are intact, profuse diuresis ensues. This we interpret as evidence that the fluid is transferred to a region where protein can be removed by the lymphatics. We had hoped that after this procedure the increment of protein in the blood stream would be demonstrable. Although between 3 and 4 liters of fluid, containing 120 to 160 gm. of protein, were dumped out of one subject, his serum proteins, to our great disappointment, did not change. In retrospect, in the light of Whipple's (9) work, our expectations were unfounded. If an excess of serum protein is introduced into the blood when there is no deficiency of serum protein, the increment is removed with great rapidity. It remains to be discovered whether it is abstracted from the blood by the tissues in general or segregated in those organs in which protein is free to escape from the circulation.

It has been demonstrated repeatedly that, in surgical shock, as blood pressure and blood flow diminish, not only does blood volume fall from increased transudation of fluid through the capillary walls, but also protein escapes from the circulation. This has given rise to the conception that the permeability of the capillaries in the circulation in general is increased. Actual evidence to support this is scanty. Of course, in a traumatized part, direct injury to the vessels may permit local extravasation not only of proteins, but even of whole blood. The theory of increased permeability, however, implies more than this; it implies that secondary vasomotor changes lead to a general increase of capillary permeability throughout the entire circulation. Freeman seems to have adopted this view in the face of evidence to the contrary, and has endeavored, with little success, to demonstrate, in blood from traumatized limbs, substances that have a specific effect upon the permeability of peripheral vessels. In his own experiments he detected no extravasation of dye in the peripheral tissues, only extreme pooling of the dye in the upper abdominal organs which are supplied by capillaries that presumably are always permeable to protein. It would be presumptuous to propose any theory of my own concerning shock; but there is no impropriety in demanding that any theory that is propounded include and adhere to all the facts that are available.

That a true increase of permeability of the peripheral capillaries can be detected by means of dyes is attested by the experiences of Ferrebee, Leigh and Berliner (22). When one of the dogs used for their experiments, who had received an injection of T 1824, developed urticaria, the wheals all turned blue. This supports an earlier observation of Govaerts (23), recently verified by

Schales, Ebert and Stead (24), that, in angioneurotic edema or serum sickness, the transudate contains a relatively high concentration of protein.

The vehicular properties of the serum proteins are not confined to the transportation of inert colloidal materials that adhere to them. Analyses of serum for iodine have proved to have great value in the diagnosis and management of patients with diseases of the thyroid. The common tests cannot, however, be applied to subjects who have received inorganic iodine for therapeutic purposes because they cannot distinguish the exogenous inorganic iodine from the endogenous hormonal iodine. Investigations of Salter (25, 26), Trevorrow (27), Man (28) and others have proved that the physiologically active iodine in blood serum is probably adsorbed upon or chemically united with the proteins. Man (29) has recently shown that this fraction can be precipitated with the proteins by the Somogyi zinc sulfate method, and that the precipitate can be washed free of inorganic iodine without loss of hormonal iodine. It is, therefore, possible, by this procedure, to measure the active iodine in the blood of patients who have received inorganic iodine. Thyroxine itself is not precipitated from aqueous solution by this technique; but if it is added to serum, either *in vitro* or *in vivo*, it adheres to the proteins just as native hormonal iodine does, and cannot be washed out of the protein precipitate. Parenthetically it is worth mentioning that the method is inapplicable to patients who have received the dyes commonly used to visualize the gall-bladder. These dyes are so firmly attached to the proteins that they cannot be removed from the precipitate by washing. Moreover, after a gall-bladder x-ray enough remains in the serum to vitiate analyses for precipitable iodine for weeks, and even months.

It was stated above that evidence is gradually accumulating that serum albumin is not an inert colloid provided in the circulation merely for the sake of its osmotic pressure. It may be susceptible of utilization for nutritive purposes. The conventional doctrine that proteins must be broken down into their constituent amino acids before they can be used must probably be revised. Schoenheimer (30) showed that serum proteins and tissue proteins are continually changing aggregations of amino acids, not fixed structural units. The conventional doctrine that in the alimentary canal digestion of protein proceeds to completion and that only amino acids are absorbed is incompatible with Salter's (31) observations about the potency of thyroid derivatives. If thyroglobulin or whole thyroid substance is given to myxedematous subjects, its potency is far greater than that of the amino acids of which it is composed. Analogous to this is the immunization of infants to certain diseases by the oral administration of placental proteins, although hydrolysates of the same proteins confer no immunity (32). These facts seem to require that the products of protein digestion are absorbed, at least in part, not as separate amino acids, but as aggregates of amino acids unless it is assumed that such aggregates burst at the surface of the intestinal mucosa, jump through together, and immediately cohere again as if they were united by rubber bands. Furthermore, these families or aggregates must retain their identity in the blood stream, presumably in the bodies of serum proteins; and from these proteins or in these proteins they must

find their way to the cells in which they act. It is implicit in Man's and Salter's experiments that the thyroid hormone is conveyed in this manner. Salter (33), indeed, has confirmed earlier observations of Abelin (34) that iodized serum albumin has all the properties of the native hormone of the thyroid. Endocrine products like insulin, that have the characteristics of protein, may be conveyed in a similar manner.

It has long been recognized that fractions of both calcium and magnesium of serum form undissociated or slightly dissociated compounds with protein and are thereby rendered non-filtrable. The nature of the calcium-protein compounds and their relation to processes of calcification have been extensively studied by McLean and Hastings (35), Greenberg (36) and others. Far more calcium is bound by albumin than by globulin. The non-diffusible calcium is proportional to the concentration of protein. Calcium, therefore, appears to combine with albumin and globulin in definite proportions, as if it followed the law of mass action. It was, at first, tacitly assumed that magnesium probably followed similar laws and that the tendency to form undissociated protein salts was a property shared by all the bivalent metals. Soffer (37), however, has recently reported that in hyperthyroidism non-filtrable magnesium is greatly increased, while in myxedema the magnesium becomes almost completely filtrable. These observations have been amply confirmed by Lavietes and Dine (38) in our laboratories. The filtrability of calcium is quite unaffected by diseases of the thyroid. Moreover, although the concentrations of calcium and protein in the serum are directly related to one another, neither total nor non-diffusible magnesium have any detectable relation to the concentration or pattern of the serum proteins. In fact, diseases of the thyroid are not characterized by any recognisable peculiarities in the serum protein pattern. It must be concluded, therefore, that the presence of the thyroid hormone in the blood stream so alters some or all of the proteins that they develop a special affinity for magnesium. Nevertheless, this modification of the proteins is of so subtle a nature that it does not affect their reactions to the analytical procedures commonly employed for their fractional measurement.

This brings out one of the most distinctive features of the serum proteins. Because of their size and complexity, subtle distinctions in the composition of these compounds defy orthodox methods of analysis. The principles underlying the techniques which are commonly employed to fractionate them divide them into gross categories according to molecular size or other physical properties. By means of the ultracentrifuge and electrophoretic apparatus further rough subdivision has been effected. But even these instruments give answers that are crude compared with the fine discriminations of which hints are found in biological reactions like those which have been discussed and in immunological responses. Among the globulins can be recognized subgroups which are quantitatively altered in various diseases. For example, globulins are increased in cirrhosis of the liver, in myelomatosis, in lymphogranuloma inguinalis and in kala azar. Clinical tests which depend on this fact were introduced, even before the rationale of the tests was comprehended; the Takata Ara test for

cirrhosis, Ray's hemolytic test for kala azar, and the formol gel test for myelomatosis. Valuable information can be secured from fractional analysis of proteins that goes no further than the partition of albumin from globulin. But methods must be found that will draw finer distinctions. There is reason to suspect that even high-powered physicochemical apparatus are unable to detect the minute differentiation practised by nature and that these infinitesimal distinctions have physiological and pathological significance out of all proportion to their magnitude.

Current opinions concerning the origin of the serum proteins I must mention with hesitation. Information on the subject is extremely scanty. It has been established with reasonable certainty that fibrinogen is formed by the liver. With far less evidence the manufacture of other proteins has been attributed to the same organ—as if the poor old liver had not enough to do already. Since certain of the globulins increase in the serum in advanced cirrhosis of the liver and other conditions associated with massive destruction of this organ, it seems more logical to seek their origins elsewhere. More must, however, be learned of the nature and functions of the various globulin fractions before they can be discussed with profit. Magnus-Levy (39) from inferential evidence, believes that the euglobulin which accumulates in the serum in myelomatosis, as well as the Bence-Jones protein which appears in the urine and the peculiar amyloid deposits sometimes found in the tissues in this disease, all emanate from the bone-marrow. Albumin has been ascribed to the liver because its regeneration is retarded by severe injury to this organ. Studies of experimental cirrhosis by Mann (40) and his associates suggest a somewhat different interpretation. They found that if dogs with experimental cirrhosis were fed diets containing large quantities of carbohydrate and milk proteins they remained in excellent condition. If they were fed on meat, they developed jaundice, hypoalbuminemia and ascites. This might seem, at first, to support Whipple's theory. Analyses of the urine during this toxic state, however, revealed negative nitrogen balances despite the high protein diets. The serum albumin deficiency may, therefore, be only a mark of protein starvation not directly connected with functional impairment of the liver.

If this discussion has wandered into unconventional and unexpected channels, if it has contributed little that is immediately applicable to the solution of clinical problems, I hope it has not been entirely disappointing. Medicine is always in danger of adopting a narrow utilitarian view; its attitude towards the serum proteins as clinical aids is tending to crystallize. This subject is new; the implications of physiological work must be appreciated and incorporated into clinical practice.

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STATUS ANGINOSUS DUE TO PROFOUND ANEMIA

Complete Relief following Resection of Gastric and Sigmoid Carcinomata

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It has long been recognized that severe and protracted anemia, either primary or secondary, can produce significant physical changes in the heart. Profound depression of circulating hemoglobin frequently induces dyspnea and palpitation and signs of cardiac enlargement, chiefly due to dilatation. So-called "hemic" murmurs are often encountered. The histologic picture in extreme conditions is characterized by "tigering" and, at times, extensive fatty infiltration. Although the electrocardiogram is by no means diagnostic, frequent P wave changes and occasional S-T segment depressions have been observed; diminished voltage is common. The electrocardiographic changes are often proportionate to the degree of anemia and tend to return to normal with improvement in the blood picture. Severe anemia thus adds a distinct burden to a diseased heart or to a normal heart laboring under the added strain of hypertension, pregnancy, or Graves' disease. The resultant increased cardiac output augments a load sufficient to produce cardiac failure.

Herrick and Nuzum (1) in 1918 made the important observation that anemia may produce cardiac pain and cited four instances of angina pectoris associated with severe primary or secondary anemia. Although three of the cases died, autopsies were not obtained. It was suggested that anemic blood traversing narrowed coronary arteries might produce angina more easily than normal blood passing through the same arteries. On the theory of relative myocardial ischemia, the threshold of pain is lowered, becoming manifest on even slight provocation. Coombs (2) in an analysis of 36 cases of pernicious anemia found the combination in 8 instances. These observers and others (5, 8, 9, 10, 11, 12, 13) noted that the intensity of the angina varied directly with the degree of anemia and that pain frequently disappeared with elevation in the blood hemoglobin content.

Remarkable circulatory efficiency is maintained in most cases of anemia due to the introduction of such compensatory mechanisms as increase in minute volume, acceleration of the blood flow due to its diminished viscosity, and contraction of the skin capillaries with consequent increase of blood flow in other organs. Fahr and Ronzone (3) after calculating the work of the heart concluded that in severe anemia the coronary circulation is taxed to the upper limit and is comparable to that expended in strenuous work; in the presence of narrowed coronary vessels the adaptive capacity may be exceeded with the production of angina pectoris due to anoxemia. Elliot (6) reported the necropsy of a case of severe anemia with angina pectoris in which the coronary arteries were free of disease. He concluded that anoxemia can produce cardiac pain in

the absence of coronary disease in certain instances of profound anemia. Willius (4) and Cabot (5) reported similar instances of freedom from coronary disease at autopsy.

Fishberg (10) has summarized the physiological mechanism for the production of anginal pain especially with preexistent coronary narrowing as follows: 1) The increased cardiac output increases the work of the heart and hence the volume of required blood. 2) The hypertrophied heart requires more blood flow. 3) There is lack of oxygen in the myocardium due to the anemia and 4) in severe anemia, the lowered arterial pressure interferes with coronary filling and the increased pulse rate curtails the rest period of the heart.

Willius and Giffin (4) analyzed 1,560 patients with pernicious anemia and found 43 cases with angina pectoris. The average age of the patient with an anginal syndrome was 53.5 years and 56 per cent occurred in the sixth decade. The one autopsy in this group was not conclusive but in three post-mortem examinations of cases of pernicious anemia with marked disease of the coronary arteries, none of the patients had complained of angina. They conclude that the anginal syndrome in pernicious anemia is due to myocardial anoxemia and not to coronary sclerosis. On the other hand, White (12), Levine (11), Fishberg (10) and Porter (9) emphatically state that coronary artery disease is almost invariably present in the cardiac pain of severe anemia and White (12) states that it has never been proven that anemia alone is responsible.

CASE REPORT

History (Adm. 451198). A 62 year old tailor was admitted to the Medical Service of The Mount Sinai Hospital on January 15, 1940. Retrosternal compressing pains radiating to the left arm and occasionally to the neck and lower jaw had appeared two and one-half years preceding admission. The distress, at its inception, was solely exertional and invariably relieved by nitrites. Within a month after the pain appeared, his family noted that his previous ruddiness was replaced by slight pallor. The stenocardia gradually increased in severity so that in the last six months it was precipitated on even slight effort or emotional stress with occasional episodes even when at rest. There was no significant weight loss, bowel function remained unaltered but he complained of anorexia and intermittent nausea. He consulted a physician in December 1939 who found his hemoglobin to be 46 per cent and interpreted the picture as that of pernicious anemia. He received 18 liver injections in the following three weeks. In spite of this therapy he rapidly became dyspneic, ankle edema appeared, syncopal seizures were frequent, and he lapsed into a true *status anginosus* with only transient relief with nitroglycerin. He was repeatedly awakened by excruciating substernal gripping pains which were devastating to his morale.

Examination: On admission he complained bitterly of cardiac pain. His nutrition was fair but he presented a profound yellowish color. There was no adenopathy. The heart was not perceptibly enlarged and the apical impulse was palpated in the fifth left interspace in the midclavicular line. The heart sounds were regular, 72 per minute, with slight accentuation of the aortic second sound. There was a localized soft apical systolic murmur. The peripheral vessels were easily compressible. The blood pressure was 124 systolic and 78 diastolic. The electrocardiogram disclosed very slight depression of the S-T segments in leads I and II and minimal QRS slurring. On fluoroscopy, the heart was somewhat transverse with moderate enlargement of the left ventricle and slight aortic widening. This configuration was essentially unaltered throughout the entire period of observation. The blood examination was as follows: Hemoglobin 28 per cent; red blood

cells 2.2 million; leucocytes 4.7 thousand with a differential count of 72 per cent polymorphonuclear leucocytes with 8 per cent non-segmented forms; 4 per cent large monocytes, 18 per cent lymphocytes, and 5 per cent monocytes. The picture was that of a profound microcytic anemia. The absence of disturbed circulatory dynamics characteristic of an overactive or dilated heart, suggested an underlying coronary artery sclerosis with diminished capacity to compensate for the reduction in blood oxygen carrying capacity, consequent upon the anemia.

Course: On the day following admission he received a transfusion of 500 cc. of whole blood which was followed by striking improvement in his symptoms although the hemoglobin rose to but 36 per cent. The cardiac pain which had plagued him unremittingly for two years disappeared and he was able to walk about the ward without distress. His appetite returned and he was able to sleep soundly. Following three transfusions the hemoglobin rose rapidly to 75 per cent. At this time even prolonged effort failed to elicit chest pain. In an attempt to determine the source of the anemia, a sigmoidoscopy was performed and a small polypoid lesion 6 inches from the anal orifice was disclosed; at biopsy it was proven to be a papillary adenocarcinoma. The patient was accordingly transferred to the Surgical Service without further investigation of the intestinal tract.

On the Surgical Service a number of interesting diagnostic and therapeutic considerations arose. It was difficult to believe that the small lesion in the sigmoid was the sole cause of the profound anemia. There had been no history of gross hemorrhage, a phenomenon which would have been almost inevitable with a lesion situated so close to the anus. Furthermore the tumor was so small and the intestinal symptoms so mild that the assumption that the anemia was part of the picture of carcinomatous cachexia because of this lesion alone was hardly warranted. Inasmuch as simultaneous multiple malignant lesions not uncommonly occur in the colon, an unrecognized neoplasm in the right colon which could account for such advanced anemia was suspected. A barium enema, however, failed to reveal any additional involvement in the lower tract. Abdominal exploration was therefore undertaken.

Operation: A laparotomy was performed through a lower abdominal incision. The tumor was easily located a few inches above the peritoneal reflexion of the rectum. It was small, about the size of a hazelnut, and freely movable although not pedunculated. Its characteristics were such that it became evident at once that it could scarcely be the sole explanation of the clinical manifestations. After further investigation, a large carcinoma involving the anterior wall and greater curvature of the body of the stomach was found. This lesion appeared to be the more probable cause of the profound anemia than the sigmoid tumor, and its resection was considered an immediate necessity, leaving the smaller sigmoid neoplasm for subsequent removal. It was felt that the patient would not tolerate both procedures and that the preliminary removal of the colonic growth might result in infection, thus delaying the approach to the more advanced gastric lesion. Following the closure of the lower abdominal incision a new median epigastric incision was made, and a subtotal gastrectomy with an antecolic Hofmeister anastomosis was performed. The resected specimen was reported as an "infiltrating adenocarcinoma of the stomach with involvement of the lymph nodes." After the first few days convalescence was extraordinarily uneventful.

Six weeks later, excision of the recto-sigmoid lesion was undertaken. Under ordinary circumstances, the preferred approach would have been either an abdomino-perineal résection or a multiple stage removal with end-to-end anastomosis. However, in view of the advanced character of the gastric lesion and the relatively early phase of the one in the sigmoid, the orthodox approach with its prolonged convalescence appeared inadvisable. Accordingly, a new median lower abdominal incision was made and the sigmoid opened vertically about 2 inches above the peritoneal reflexion. Through this opening, the tumor, which proved to be about the size of a hazelnut, located on the posterior wall, was delivered. It was sessile but a pedicle could be made of the non-infiltrated mucosa on the posterior wall. This pedicle which measured about $\frac{3}{4} \times \frac{1}{2}$ inch was clamped

with fine forceps. The tumor was removed and hemostasis and closure secured by oversewing the clamp with fine silk sutures. The vertical incision in the anterior wall of the sigmoid was then closed transversely and the suture line buttressed and shut off from the general peritoneal cavity by obliterating the *cul de sac* to a level about 1 cm. above the suture line. This was accomplished in a manner similar to that used in the Moschcowitz operation for rectal prolapse. A cigarette drain was inserted down to the pelvis and the wound closed. Recovery was uneventful with primary union of the wound. It is noteworthy that at no time during the course of these major operative procedures did the patient experience any anginal pain. The hemoglobin, throughout this entire period, was never permitted to fall below 60 per cent.

Follow-up: Following discharge from the hospital the patient gradually resumed his previous occupation as a tailor which necessitated long hours, a half mile walk to and from the subway in all types of weather and the climbing of many flights of stairs. In spite of this, he has been singularly free of discomfort and has not experienced any episodes of cardiac pain. There have also been no gastric or intestinal symptoms. When last seen in July, 1942, he was in excellent condition, he had gained 25 pounds in weight, the hemoglobin was stationary at 86 per cent and x-ray examination of the colon and stomach revealed no abnormality. Sigmoidoscopy disclosed no evidence of recurrence.

COMMENT

The appearance of angina pectoris in severe anemia may be linked to a substratum of coronary artery sclerosis. Its incidence is extremely rare in profound anemias of youthful individuals. A great majority of the instances of cardiac pain found in connection with pernicious anemia (4) or carcinoma appear in the age group in which coronary sclerosis has begun to compromise the capacity of the myocardium to bear an added burden. Isolated instances of true angina pectoris without significant coronary artery disease at necropsy have been reported. The theory that anoxemia alone, in the absence of coronary disease, can produce angina pectoris is questioned by White (12) who does not feel that anemia can be deemed responsible for the attacks nor that it is even an important factor. Levine (11) recognizes that in a heart otherwise structurally sound and competent the lowering of the hemoglobin content below 20 per cent can produce a state of relative anoxemia with consequent cardiac pain.

The dyspnea on exertion, palpitation and precordial awareness, if not oppression, that many profoundly anemic subjects experience must be distinguished from the classical anginal seizure with true *dolor animi*, hyperhidrosis and intense anxiety. If, in addition, there is a marked degree of cardiac hypertrophy, the adaptive limit of the coronary flow in anemia is often easily exceeded. The critical level for the appearance of anginal pain varies widely and, frequently, at different times in the same individual.

SUMMARY

1. Angina pectoris of increasing severity appeared in a 62 year old man suffering with profound anemia due to two independent gastro-intestinal neoplasms.

2. The cardiac pain was promptly relieved following transfusions and never

recurred in spite of two operative procedures and the resumption of full activity.

3. Angina pectoris in profound anemia may be superimposed on coronary artery disease with consequent limitation in vascular adjustment to the anoxemia induced by the diminished blood oxygen carrying capacity.

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TATTOOING WITH MERCURY SULFIDE FOR INTRACTABLE ANOGENITAL PRURITUS, WITH SPECIAL REFERENCE TO LEUKOPLAKIA-KRAUROSIS

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Therapeutic tattooing with mercury sulfide for intractable and pernicious pruritus ani has yielded encouraging results except in some patients who had had excessive roentgen irradiation of the perianal skin. Pruritus perinei (with or without involvement of the posterior vulva) caused by an extension of anal pruritus also responds well to this form of therapy (1). Tattooing with mercury sulfide produces a functional impairment of the cutaneous sensory terminals by reducing their capacity to respond to adequate stimuli (1). The change in the sensory modalities which is produced is proportional to the amount of intracutaneous deposit of mercury sulfide. The mechanical trauma alone produced by the tattooing machine without the deposition of mercury sulfide or the substitution of several other chemicals was ineffective in relieving pruritus ani permanently; apparently the psychic effect of tattooing is of no therapeutic value in relieving pruritus ani.

Histologic studies of therapeutically tattooed skin with mercury sulfide showed no deleterious effects upon the skin; a foreign body giant cell reaction commonly seen after the intracutaneous introduction of other foreign bodies has not been observed after tattooing with mercury sulfide (2).

Selected cases of hitherto intractable pruritus vulvae and ani which had been treated successfully by tattooing with mercury sulfide (after other therapy had failed) are discussed here in detail. Particular attention is called to the effectiveness of this form of therapy in selected cases of pruritus of leukoplakia-kraurosis.

CASE REPORTS

Case 1. History (O.P.D. 36-7663). A. R., a 63 year old white woman had had pruritus ani, perinei and vulvae of about fifteen years' duration. Menopause had occurred at the age of 47 years. The patient had received radiation therapy to the vulva in 1928 and to the perianal region in 1931. Since August 1936, she had received eleven additional courses of roentgen irradiation to the vulva and perineum. On January 20, 1937, it was noted that the anal itching was intense and that in May 1938, the itching in the posterior aspect of the vulva was becoming worse. She had also had a variety of treatments other than roentgen-ray; all without avail. This patient was seen by me for the first time in August 1939, and tattooing of the circumanal area and the posterior aspects of the vulva with mercury sulfide was advised. This was carried out in two sittings (August 11 and September 1, 1939) under procaine hydrochloride infiltration anesthesia. Subsequently, several skipped areas were discernible on the left anoperineal aspect which were subject to intermittently recurring mild pruritus. On August 16, 1940, about a year following tattooing, biopsies of skin from each anoperineal side were performed for histologic studies. The adequately tattooed non-pruritic right side showed a uniform distribution of the intracutaneously deposited mercury sulfide while the opposite incompletely tattooed left ano-

perineal side (skipped areas) in which some intermittent pruritus recurred, revealed areas that had either no mercury sulfide or an uneven scant deposit (2). A study of the cutaneous modalities revealed a diminution of pain and tactile sensation on the adequately tattooed right side which was free from recurrence of pruritus. The patient continued to have occasional mild pruritus confined to the left anoperineal side; this region was therefore retattooed with mercury sulfide on March 21, 1941. Pruritus vulvae has been absent since the primary tattooing of the perianal and perineal areas.

Comment. The incidence of "skipped" areas where localized areal pruritus may continue and which is erroneously regarded as a recurrence of the pruritus depends on the skill and experience of the operator. In spite of special care and precautions (3) it is at times impossible to avoid skipping small areas of involved skin. These can however be retattooed at a subsequent time, if necessary. The correlation between adequate tattooing with mercury sulfide and the diminution of the cutaneous modalities is again illustrated in this case.

Because the anal and perineal pruritus was intense in character, treatment was first directed to the perineum and perianal circumference only; this resulted in the disappearance of the anoperineal as well as of the vulval pruritus. Other similar experiences have been described elsewhere (1).

Case 2. History (O.P.D. 33-3862). M. B., a 56 year old woman, had had pruritus ani, perinei and vulvae for over four years which had failed to respond to the excision of infected anal crypts (Morgagni) performed on September 27, 1939, and to subsequent radiation therapy to the perianal region. Endocrine and topical therapy were also ineffectual in relieving the itching. Examination revealed atrophy of the mons veneris, labia majora, perineum and the perianal skin. A biopsy of the vulval skin was performed on December 9, 1939; the histologic examination revealed hyperkeratosis and degeneration with hyalinization of the subepithelial zone. The patient was first seen by the writer in December 1939 and a trial of therapeutic tattooing with mercury sulfide of the anogenital area was advised. Accordingly, the perineum was tattooed on January 3, 1940, and the perianal and anal regions six days later. On March 8, she developed an eczema on the vulva which extended to and stopped sharply at the tattooed perineum. About ten months after tattooing there appeared two superficial fissures in the perineum, which extended to the anal orifice causing pain on defecation and during walking but no pruritus. On January 10, 1941, a small round patch of dermatitis occurred in the right crural region which recurred on March 3 with involvement of the opposite crural fold and of the vulva. The vulval lesion again stopped abruptly and sharply at the line of the tattoo.

Comment. The occurrence of superficial fissures in the tattooed areas has been noted in other patients (1). These lesions usually respond to topical applications of bland ointments or silver nitrate, but occasionally may require small dosages of superficial radiation therapy. At times these fissures constitute trigger points for recurrent pruritus. To date they have not been a serious therapeutic problem.

An interesting feature in this case is the sharp arrest of the spread of the recurring vulval eczematoid process at the line of the tattooed skin.

The tattooing of the vulva of this patient has been deferred because in the absence of vulval dermatitis, pruritus vulvae has been either absent or mild in character since the tattooing of the perineum and the circumanal area.

Case 3. History (O.P.D. 34-16582). S. H., a 46 year old, normally menstruating woman was seen in April 1939, because of pruritus vulvae, perinei and ani. The anal itching had definitely preceded the genital pruritus. Treatment given elsewhere was ineffectual. Examination was normal except for thickened and folded perianal skin and internal piles. The latter had been treated by the injection of a sclerosing solution. The entire vulva and most of the perineum were tattooed with mercury sulfide on May 26, 1939. Because of the difficulty in tattooing the cutaneous folds about the clitoris, many areas of skin were "skipped" in this region (figs. 1, 2). The vulval pruritus disappeared except for the intermittent recurrence of mild itching about the clitoris. The anal pruritus continued and was definitely aggravated immediately before and after menstruation. On December 6,

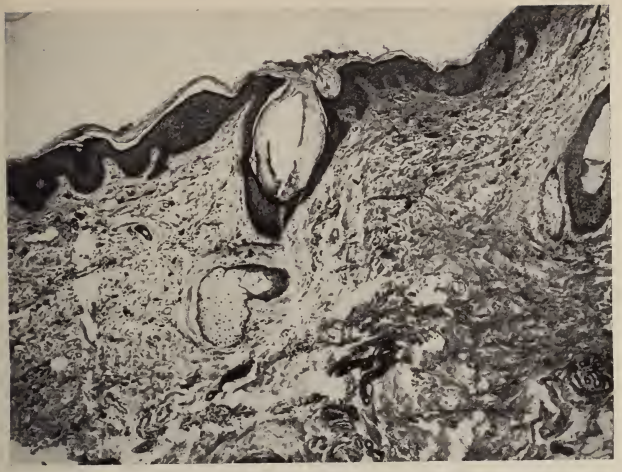

FIG. 1. A section of vulval skin (skipped areas) six months after tattooing, shows areas that have either no mercury sulfide or a sparse deposit

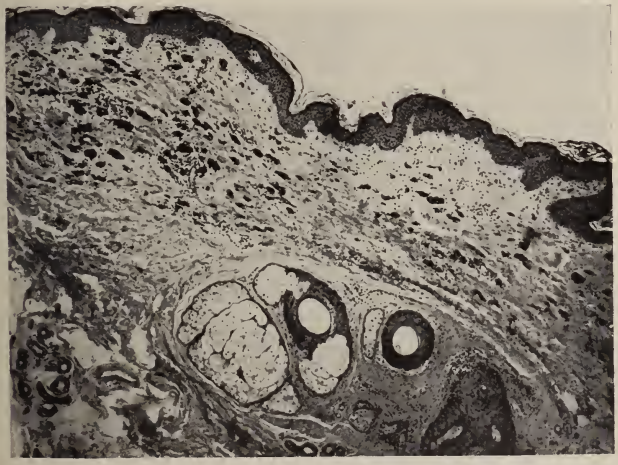

FIG. 2. A section of better tattooed vulval skin from the same patient twelve months after tattooing, shows by contrast an abundant subepithelial deposit of mercury sulfide on the left side. Note the absence of foreign body giant cell reaction in both sections.

1940, eighteen months after tattooing the vulva and the perineum, the patient complained of unusually severe anal pruritus. (A section of the perianal skin was removed for histologic study and showed evidence of chronic inflammation). The perianal and anal regions were tattooed with mercury sulfide on January 17, 1941. To date, she has remained practically free from pruritus in the anogenital region.

Comment. In this instance the entire vulva and most of the perineum were tattooed in one sitting. The deep cutaneous folds about the clitoris could not be held taut sufficiently long to allow the proper penetration of the needles and the chemical. The resulting skipped areas are subject to intermittent localized mild pruritus. In spite of this, the patient felt sufficiently well so that retattooing of the skipped areas was deemed unnecessary.

The anal pruritus was purposely ignored in order to make comparative observations on the progress of the untreated anal skin and the effect of the intracutaneous mercury sulfide on the treated genital skin. About twenty months after tattooing of the vulva and the anterior portion of the perineum, the anal pruritus had become unbearable, necessitating the tattooing of the perianal and anal regions. To date, the patient has been practically free from anogenital pruritus.

Case 4. History (O.P.D. 34-18102). B. G., a 64 year old white woman, had had pruritus vulvae for over four years. Menopause had occurred at the age of 50 years. Atrophy of the vulva and vagina was discernible on January 30, 1937. In June 1939, vulvectomy was advised and refused. The patient was seen by the writer for the first time on April 5, 1940, when she still complained of severe pruritus in the anterior aspect of the vulva about the area of the clitoris and mons veneris. Examination showed moderate atrophy and leukoplakia of the anterior portions of the labia majora and about the clitoris. A biopsy of the skin on the left side of the level of the clitoris was performed; the histologic examination revealed changes consistent with leukoplakia-kraurosis vulvae (local atrophy and hyperkeratosis of epidermis, acute and chronic inflammation of corium and atrophy of elastica of corium). Vulvectomy was again advised and refused. The area of definite pruritus was then delineated and about two-thirds of the vulva (excepting the posterior portion) were tattooed with mercury sulfide on May 10, 1940. She continued to have mild pruritus in the tattooed areas especially at night and after bathing in hot water. Subsequently the pruritus was localized to a small area above the clitoris which was the site of an abrasion. On August 2, 1940, the patient began to complain of pruritus in the untattooed posterior portion of the vulva. A section of skin removed from this area showed no significant changes on histologic examination. On September 6, the posterior aspect of the vulva and the anterior part of the perineum were tattooed with mercury sulfide. After the subsidence of the usual post tattoo reaction, the patient continued to be free from pruritus during the day but she had some itching at night and after taking hot baths. A number of biopsies of the skin had been performed from time to time to observe possible cutaneous changes; no deleterious effects have been observed. The sites of the biopsies, however, healed slowly; the scars being devoid of mercury sulfide are subject to intermittent mild pruritus. The last histologic study of a section of tattooed skin made five months after tattooing also showed no deleterious effects on the skin and an absence of foreign body giant cell reaction. Subsequent histologic studies of the tattooed skin have not been made because of the slow healing of the wound and temporary return of marked pruritus at the site of biopsy which always disturbed the patient. On November 14, 1940, the patient stated that she had had no pruritus vulvae for some time except after taking a hot tub bath. On March 14, 1941, ten months after the original tattooing, she reported that pruritus no longer occurred after bathing in hot water. The patient's general health improved and she gained over ten pounds in weight. On May 2, 1941, there appeared moderate pruritus in the untreated right side of the perianal region as well as in the tattooed right labium majus. The right perianal region was therefore tattooed on May 27. At the same time the right labium majus was retattooed. This was followed by the disappearance of the pruritus.

Comment. Because leukoplakia-kraurosis vulvae has a tendency to undergo malignant changes (4) in many cases (especially when fissures are present) vulvectomy was urged in this case even in the absence of cutaneous fissures. Since the patient refused the operation, tattooing with mercury sulfide was given a therapeutic trial with the understanding that frequent and prolonged observation will be necessary. To date, no deleterious cutaneous effects have been observed.

The anterior portion of the vulva which was the site of severe itching and which showed histologic evidence of leukoplakia-kraurosis was tattooed first. The immediate result was the practical arrest of irritation and scratching and the almost complete cessation of pruritus. Subsequently, the posterior portion of the vulva was tattooed with mercury sulfide because of the later development of itching in that area. (The histologic examination of skin from this posterior area revealed no significant cutaneous changes.) Ten months after the tattooing of the anterior vulva, all pruritus including the itching following bathing in hot water disappeared. The result of this procedure to date in this patient has been the relief from pruritus and irritation and the elimination of continuous trauma incident to scratching.

The therapeutic results obtained in this case have been duplicated in another patient with leukoplakia-kraurosis vulvae.

Case 5. History. (Adm. 441304)[1]. L. S., a 32 year old white woman, gravida and para 3, was admitted to the hospital on January 15, 1936, because of intense pruritus vulvae and ani. The menstrual periods were regular and normal. She had been seen in the Out-Patient Department on January 6, 1934, because of constipation, pain on defecation and pruritus ani. At that time the rectal examination revealed tenderness on digital exploration as well as perianal and perineal fissures. Late in 1935 an atrophic vaginitis with maceration of the labia was discernible which had failed to respond to conservative treatment. Physical examination on this admission was normal except for atrophy with fissuring and maceration of the tissues involving the clitoris, the upper margin of the urethra, the labia minora, the fourchette and the perineum. Because the intense pruritus had not been relieved by estrogenic therapy and hygienic measures, a partial vulvectomy was performed without removing the perineal skin. The histologic examination of the excised specimen revealed hyperkeratosis, chronic inflammation and disappearance of elastic fibers of the corium; these cutaneous changes are consistent with the diagnosis of leukoplakia-kraurosis.

The patient was readmitted to the hospital on May 15, 1936, because of severe pruritus ani and perinei. Three days later, a wide excision of the perineal skin was effected (completing the two-stage vulvectomy). The histologic examination of the excised specimen showed leukoplakia and chronic inflammation.

The patient was well for about two months when she developed recurrent anogenital pruritus which was particularly intense on the left side of the introitus, necessitating admission to the hospital (January 26, 1938). Examination revealed a thickened and a yellowish white area with deep fissures in the perineum, and atrophy along the left side of the introitus, extending to the anal region. The vagina admitted two fingers, was soft, and resilient. At this time, the involved skin of the left side of the introitus and of the perineum was removed. The histologic examination of the excised tissue revealed leukoplakia-kraurosis.

The patient remained free from pruritus until June, 1938 (a period of four months), when she experienced a recurrence of the itching and burning in the introitus, the intensity of which was increased during the menses. Examination showed a normal uterus and adnexae. There was atrophy of the skin adjacent to the clitoris and a recurrence of the kraurotic-like process at the vaginoperineal junction. As a result of the previous operative procedures, the posterior vaginal mucosa had extended over the upper one-third of the perineum. At its distal portion, it was partially epithelialized and atrophic. In

[1] Previously reported in part, Am. J. Obst. & Gynec., 40: 334, 1940.

the intergluteal region there was a bilateral, symmetrical area of parchment-like atrophic skin which extended to and encircled the anus. On October 19, 1938, the atrophic skin of the subclitoric region, and the kraurotic-like process at the vagino-perineal junction was removed. The histologic examination of the excised skin showed areas of chronic non-specific inflammation without evidence of kraurosis. On November 10, several Thiersch grafts were implanted upon the granulating perineal area.

There was continuous itching and soreness in the region about the left side of the introitus and in the entire perianal area. Reexamination on June 5, 1939, showed a narrowing of the introitus and a whitish plaque about the anterior commissure. The skin of the posterior commissure, the terminal inch of the mucosa of the vagina and the skin of the perineum extending to and surrounding the anal orifice had changed to a white, thick, cornified plaque. The perianal skin was tense, shiny white in appearance, and parchment-like in consistency. The crural folds presented the same appearance and were also fissured.

Physical examination at this time was otherwise normal; there was no evidence of disease of the nervous system to account for the local manifestations. The essential laboratory tests yielded normal findings. On June 7, 1939, the perianal and the perineal regions were tattooed with mercury sulfide under infiltration anesthesia, using one per cent solution of procaine hydrochloride according to the technique described elsewhere (3).[2] Seven days later, the vulva was similarly tattooed with mercury sulfide under avertin supplemented by infiltration anesthesia. One month later, the skin about the introitus and in the perianal region, with the exception of the perineal area, was normal in appearance. Nine months later, the patient was still free of pruritus in spite of the presence of moderate excoriation of the perineum. The perineal excoriation was believed to be caused by a continuous escape of vaginal discharge.

On July 26, 1940, about thirteen and a half months following tattooing, the patient noted burning and pain in the excoriated perineum, especially after defecation. Examination revealed vaginal discharge and a grayish-white perineum with three superficial fissures one of which extended to the anal orifice. One week later, there occurred moderate itching confined only to the perineum. Biopsies of skin were taken from the perineum and from a well tattooed non-pruritic area, 2 cm. from the site of the perineal biopsy. The histologic examination of the skin of the perineum showed a scant deposit of mercury sulfide deep in the corium, many lymphocytes and leukocytes. The skin from the well tattooed non-pruritic (control) area revealed a uniform and an abundant subepithelial deposit of mercury sulfide as well as moderate infiltration of round cells (2). Because of intermittent perineal pruritus and the gross and microscopic appearance of the perineum, the perineum was retattooed with mercury sulfide on September 11, 1940. Treatment of the vaginal discharge was again urged. Six months after retattooing the patient was still free from pruritus, but the perineum showed a beginning of fading of the red tattoo color.

Comment. Tattooing with mercury sulfide was successfully employed in this case after all available forms of therapy including several surgical procedures had failed to arrest the progress of the cutaneous lesion and to control the pernicious pruritus vulvae, perinei and ani. In this instance, tattooing with mercury sulfide proved to be an indispensable form of therapy.

SUMMARY AND CONCLUSIONS

A detailed description of a group of selected, hitherto intractable cases of pruritus vulvae et ani that responded well to tattooing with mercury sulfide is presented. This new form of therapy also was effective in primary leukoplakia-kraurosis vulvae and in recurrent leukoplakia-kraurosis following medical and

[2] I recently devised a durable, reciprocating, pneumatic tattooing pistol which has many advantages over the ornamental tattooing machines used heretofore.

surgical therapy. The application of this procedure to leukoplakia-kraurosis is still in the experimental stage and for the present is limited to primary vulval cases (without cutaneous fissuring) who refuse vulvectomy, and to the recurrent cases following adequate surgical procedures.

The therapeutic results herein recorded parallel those reported elsewhere by the author following tattooing with mercury sulfide in the treatment of a large series of cases of pernicious and intractable pruritus ani.

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LATE INFECTION OF HEALED LANE-PLATED FRACTURE OF THE FEMUR BY SALMONELLA TYPHIMURIUM

Lane Plate as Locus Minoris Resistentiae[1]

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CASE REPORT

History (Adm. 466740). This is the third admission of Mrs. K. M., an elderly woman who was aged 65 when she first came to The Mount Sinai Hospital for treatment. At that time, in June 1937, she had non-union of a fracture of the mid-shaft of the right femur. This had been treated elsewhere by Russell traction and a brace for five months (fig. 1). Bowing deformity had resulted, with pain and inability to walk. Operative drilling to stimulate union was decided upon, but after exposure of the fragments, a Sherman type of Lane plate was applied for better internal fixation. This was a long vanadium-steel plate.[a] The proximal screw could not be inserted because the bone fragments and plate could not be made to fit absolutely perfectly. Nevertheless, firm fixation was obtained, and additional chip bone grafts were applied (fig. 2).

The postoperative convalescence was absolutely uneventful. Position was well maintained in the plaster spica for almost three months. At that time, September 1937, clinical and x-ray examination showed firm union. After a few weeks in bed, she became ambulatory in her original caliper brace. The fracture became solidly healed with slight lateral bowing. There was never any trouble with the wound which healed primarily.

The brace was discarded in November 1937, five months after the operation. Knee motion of only twenty degrees of flexion from the fully extended position was obtained despite long physiotherapy. Thereafter, she got about very well with no support at home, and with a cane for walking outside. At times "rheumatic" pains were present at the operative site in the thigh and the knee. These were relieved by rest and were never severe enough to cause her to seek treatment or even return to the follow-up clinic.

One week before the present admission, she suddenly developed severe pain in the right thigh, near the old fracture site. Although there was no preceding injury or illness, there was a doubtful history of loose stools without fever immediately preceding the onset of the pain. High temperature (105°F. at home) developed with increasing pain and swelling of the thigh, and marked prostration.

Examination: The patient was acutely febrile, prostrated and confused. The right thigh was greatly swollen in its middle part. The old scar was thin, well healed, not superficially tender, about eight inches long. Marked tenderness was present in the middle third and questionable deep fluctuation was found. The shaft of the femur was solid, hip motion free, but the knee flexed only twenty degrees.

Immediate x-ray examination (fig. 3) showed the fracture to have healed completely, with moderate lateral bowing, and much cortical thickening. The plate was *in situ* and there was slight absorption of the cortex with a small area of rarefaction about the proximal screws, suggesting an abscess.

Aspiration of the thigh produced abundant thick pus, adjacent to the femur. The odor of the pus suggested an organism of the B. coli group. Blood culture was taken and immediate operation undertaken.

Operation: The old incision was opened widely and the muscles separated. No pus was found until, next to the femur, the discolored Lane plate was exposed. A

[1] Presented at a Clinical Conference, February 28, 1941.

arge amount of greenish-gray pus was evacuated extending along and around the whole plate, bathing it and extending between it and the femur and around the individual screws. The plate and all screws were removed, all were loose so they did not have to be unscrewed. The bone was superficially eroded at the site of the plate but was not deeply infiltrated

FIG. 1.

FIG. 2.

FIG. 1. (June 10, 1937.) Non-union of fracture of right femoral shaft
FIG. 2. (August 18, 1937.) Application of Lane plate immediately postoperative

except at the screw holes. Ten grams of sulfanilamide was placed in the wound, which was packed wide open.

Laboratory Data: The preoperative blood culture showed B. welchii in the liver tube, but this was thought to be a possible contaminant. A second blood culture taken two days later was negative. The pus aspirated from the thigh showed a pure culture of Salmonella typhimurium, variety Binns. Repeated wound cultures continued to

show the same organism until after the sulfanilylguanidine when it became negative, the day before discharge from the hospital. At different times, not immediately postoperative, B. welchii and B. pyocyaneus were found in the wound as secondary invaders, transiently. Repeated stool cultures from December 25 on by The Mount Sinai Hospital laboratories and the New York City Health Department showed only enterococcus and B. coli, but no unusual organisms. Urine was not cultured and showed no abnormalities.

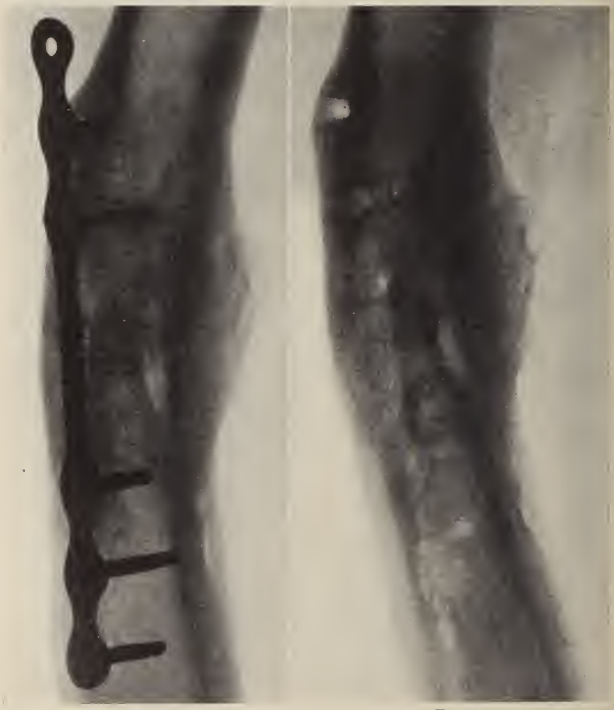

FIG. 3. FIG. 4.

FIG. 3. (December 19, 1940.) Solid union. On last admission to the hospital, at time of infection

FIG. 4. (February 6, 1941.) After removal of plates and screws

Two days postoperatively, the hemoglobin was 72 per cent and the white blood cells 7,600 per cu. mm. with a normal differential.

Course: Sulfathiazole was administered in the usual manner postoperatively, four grams at once and one gram every four hours for six days until twenty-nine grams had been given. Two days after beginning administration, the blood sulfathiazole reached 4.8 mg. per cent.

Temperature began to decrease at once with immediate improvement in the general condition of the patient. A week later the temperature was almost normal, though it reached 100+°F. at intervals until the end of the fourth week. After the first few days, the problem became that of care of a large infected thigh wound without general complications.

A cast was applied for about two weeks as a modified Orr dressing. The wound continued to discharge a great deal of pus without any actual retention in spite of the use of azochloramide. On January 24, almost a month after incision, the bone was still exposed in the depths of the wound. Ozoleum was then applied as a dressing several times. Immediate improvement in the granulations took place and discharge was much less profuse but culture of the wound still showed the original organisms. Finally, sulfanilylguanidine (10 grams) was introduced into the wound on February 8, 1941, and this sterilized the wound of the organism, at least for one culture. By the time of discharge, the wound had largely filled in with granulations and the patient was ambulatory again. Final x-ray check-up showed no change of significance except for the absence of all the metallic devices (fig. 4).

Follow-up Examination: On September 25, 1941, she was re-examined. The wound was well healed and had given her no trouble after discharge from the hospital. She walked well without support or limp. The knee flexed only twenty degrees as before. Generally she was quite well.

DISCUSSION

There are two noteworthy features of this case, the unusual organism and the presence of the plate as a reason for the late, severe and unusual localization of the infection.

1. The Salmonella typhimurium (1) is one of the paratyphoid group of organisms. The members of this group resemble each other very much, being Gram negative, motile rods. This particular organism is very closely related to the Bacillus pestis caviae, which it was called in this case in one report from the New York City Health Department. Differentiation by morphological, cultural and even sugar fermentation methods is impossible. Immunological methods, i.e., agglutination by specific antisera and agglutinin absorption, are required for final differentiation. This organism was first identified as the causative agent in mouse typhoid virus, and was soon found pathogenic for other laboratory animals. In humans, it was first found in cases of gastro-enteritis by Trommsdorf in 1903. Other food poisoning cases, the food apparently contaminated by infected mice, have been reported, with some deaths. The entire paratyphoid group is characterized by production of food poisoning and gastro-enteritis, with only rare entry into the blood stream, biliary tract or urinary system, when it can produce typhoid like lesions.

2. It is well known that internal fixation (2, 3) of fractures by metal plates and screws carries with it some risk of immediate or delayed complications apart from immediate gross wound infection and delay of union. It is not uncommon to obtain primary wound healing after such a fracture operation, followed in a few weeks or months by signs of local irritation, low grade inflammation, collection of fluid, pain and mild fever. If permitted to progress, a sinus and secondary infection may appear. Culture of the original irritative fluid is often sterile. These complications become very rare as time passes after the operation, so that after six months or a year, there is little likelihood of further trouble.

However, in some cases, even many years later, similar irritative phenomena appear, usually without gross infection or suppuration. Removal of the corroded and discolored metallic material allows immediate suture without drainage and primary healing, provided the fluid is sterile, even though it superficially resembles pus.

Apart from immediate infection and gross technical deficiencies in the internal fixation, two main reasons are given for such late complications of plate applications.

1. Electrolytic action (4) between the tissue fluids and the ordinary metals used in plates and screws, especially vanadium steel, silver, etc. This reaction is supposed to cause bone absorption around the screws thus destroying the fixation and allowing motion with all its potentialities for non-union.

This has led to the introduction of the inert alloy of chromium, cobalt and molybdenum called vitallium (5). This is at present the favorite metal for internal fixation but it has certain disadvantages and it is too soon to say whether it will be the great improvement over the older metals which we hope.

2. Inadequate fixation, either internally at the time of operation, or later, bone absorption about the screws, because of great local tension or inadequate external support, may cause the screws to loosen. Mobility will result and local irritation produce its late sequelae.

For this reason, many surgeons remove all their plates after bony union has been accomplished, especially if they are superficial (Scudder). Sherman (6) and others believe the great majority of plates cause no trouble and leave them in unless they cause trouble. Sherman says only five per cent will have to be removed. At The Mount Sinai Hospital we usually leave the plate *in situ* unless trouble in the way of local irritative symptoms supervene. Nevertheless, we remove more than five per cent. This statement, of course, applies to the older type of Sherman vanadium steel plate. From reports in the literature, the newer vitallium plates are much better tolerated, have to be removed less often and give rise to late irritation infrequently. Exploratory operations after vitallium fixation have shown firm holding of the screws after long periods, unlike the other metals.

In this patient, from all we know of the infecting organism, it must have come from the gastro-intestinal tract originally, probably as the result of a food infection. This was subclinical in the sense that no gastro-enteric history could be elicited, except some loose stools. Repeated stool cultures did not reveal the organism, indicating the original infection was transient. A temporary bacteremia must have taken place after which the organisms localized at the old plated fracture site. Can we state what caused the localization of the unusual bacillus at such a place? We have no proof but only strong suspicion. We know that the plate and screws were loose at operation; the preoperative x-ray showed rarefaction around the screws; the metal was found to be markedly blackened and corroded. These extensive changes were older than the week old acute febrile symptoms. The corrosion of the metal was undoubtedly by electrolytic action, and probably the formation of irritative fluid accompanied the loosening of the screws.

Under such circumstances, the bacteremia which might otherwise have passed off asymptomatically, lodged at the favorable spot for bacterial growth. A rapid change from a low grade irritation to a virulent infection took place, producing a large abscess requiring prompt incision and drainage.

Immediate healing without further infection of the bared bone took place. Further bone involvement would certainly have appeared if the flareup were due to a primary osteomyelitis and not to an infection of the material about the plate.

The benefit of the ozoleum was not clearly established although it seemed to cleanse the wound and stimulate granulations. The sulfanilyl-guanidine, which has been reported to have a specific effect on various enteric organisms, notably the dysentery bacillus, certainly sterilized the wound of the Salmonella, at least temporarily. It is well worthy of further trial in infections by this group of organisms.

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STUDIES ON THE OXIDATIVE DESTRUCTION OF PRESSOR AMINES

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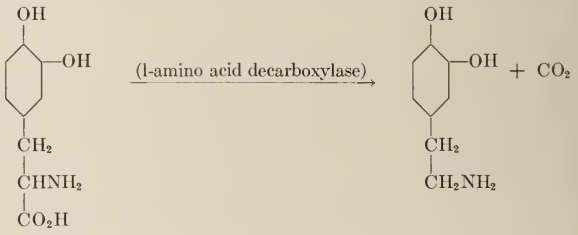
[From the Laboratories of The Mount Sinai Hospital]

There is a good deal of evidence that experimental hypertension is due to the liberation of some pressor substance or substances by the ischemic kidney into the blood stream, and it appears probable that these substances are amines. Braun-Menendez et al. (1) have shown that the venous blood from an ischemic kidney contains a substance which causes a transitory rise of blood pressure on injection into another animal. It has also been shown by Page (2) that plasma from hypertensive dogs or patients caused constriction in the isolated rabbit's ear. Concerning the possibility that these pressor substances are amines, Holtz (3) gave evidence for the presence of a l-amino acid decarboxylase in the kidney cortex. He showed that the anaerobic incubation of l-dopa with an extract of kidney cortex produced a pressor substance. This pressor substance was identified as hydroxytyramine. The reaction can be written as follows:



l-dopa hydroxytyramine

According to Holtz, hydroxytyramine was not present when l-dopa was aerobically incubated with an extract of kidney cortex. This was due to the aerobic destruction of hydroxytyramine by amine oxidase.

In vitro and in vivo decarboxylation of precursors of pressor amines by kidney cortex. The above experiments of Holtz have been substantiated by Bing (4) and ourselves not only on dopa but also on the amino acids tyrosine and phenylalanine which, on decarboxylation, give rise to the pressor amines tyramine and β-phenylethylamine, respectively. Figure 1 is an example of the difference in blood pressure rise obtained on injection of the deproteinized filtrates from anaerobically and aerobically incubated mixtures of l-tyrosine and a suspension of ground kidney cortex. It is interesting to note that pressor effects were obtained with the use of the same anaerobically incubated kidney cortex suspension to which no amino acid had been added. These effects are probably due to the

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[2] Hernsheim Fellow in Chemistry.

presence of tyrosine, phenylalanine, tryptophane or polypeptides in the kidney cortex, which give rise to pressor amines on decarboxylation. The pressor effects of the "blanks" are greatly diminished if the ground kidney cortex is first dialyzed and thus depleted of amino acids. The anaerobic formation of pressor amines from certain amino acids in the presence of kidney cortex suggests the possibility of the operation of a similar mechanism in the ischemic kidney.

Inactivation of pressor amines. Because the pressor substances of known chemical structure are all amines, the strongest being derivatives of phenylethylamine, and because of the formation of pressor amines from certain amino acids in hypertensive animals, it was thought worthwhile to attempt to find

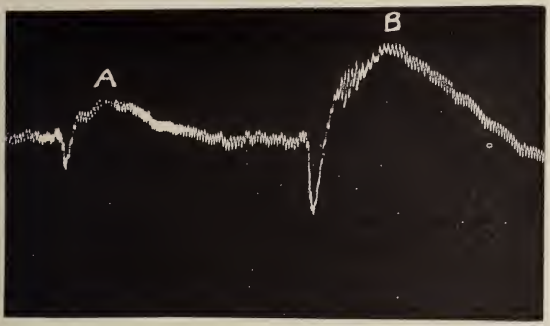


FIG. 1. Blood pressure (femoral artery) of nembutalized cat. l-Tyrosine was incubated with a suspension of kidney cortex, followed by deproteinization. (A) shows the slight rise of the blood pressure when the mixture was incubated aerobically. (B) shows a much greater rise obtained from the same mixture incubated anaerobically. Each time 1 cc. of the final solution was injected intravenously. In each case 50 grams of ground dialyzed kidney tissue were added to 50 mg. of l-tyrosine in 10 cc. of 2 per cent sodium carbonate solution. Anaerobiosis was achieved by holding the reaction mixture under nitrogen. After standing about 13 to 14 hours, the mixtures were acidified, allowed to stand in boiling water for about 5 minutes, filtered and made just alkaline with sodium bicarbonate.

agents capable of destroying amines which at the same time are therapeutically useful. The enzyme amine oxidase suggested itself for this purpose.

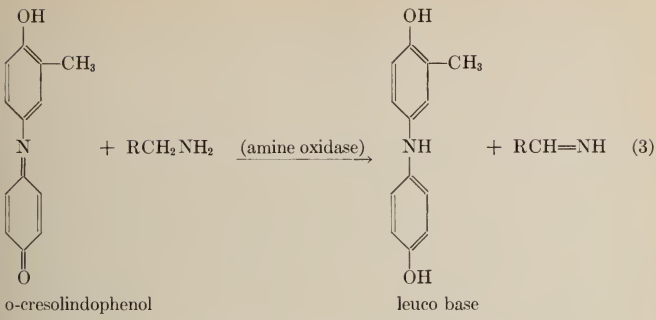
To date no water-soluble preparation of amine oxidase has been reported with the possible exception of Hare's "cell-free" extract of hog liver (5). We employed the following methods in order to obtain a water-soluble preparation of this oxidase from ground frozen hog kidney and from dried sliced hog kidney. Some of these procedures were also applied to ground frozen hog liver and dog brain. Extraction was carried out with aqueous sodium bicarbonate solution (pH 8) at 25°C. and 37°C. for two hours, or with 0.05 M acetate buffer (pH 6) at 37°C. for two hours, with 40 per cent glycerol (pH 8) or 15 per cent glycine in water (pH 8) or 1 per cent thiolactic acid in 0.05 M pyrophosphate buffer (pH 8) at 37°C. for a half hour, also with 1 per cent thioglycolic acid in 0.05 M

pyrophosphate buffer (pH 8), 1 per cent aqueous sodium cholate (pH 8) or 1 per cent aqueous solution of bile salts (pH 8).

In all of the above trials with the exception of the acetate buffer, the extracts were active when filtered through a rough filter paper so as to allow the passage of fine particles. However, after filtration through two pieces of fine filter paper, the clear solution so obtained was inactive. The second method of extraction resulted in a clear inactive solution even on passage through a rough filter. This work indicates that the enzyme is firmly attached to the tissue as in the cases of cytochrome oxidase, succinic dehydrogenase and other enzymes. Acetone, alcohol and ether dried kidney tissues are devoid of enzyme activity. Autolysis of freshly ground kidney in the presence of toluene is also destructive to amine oxidase.

To ascertain the effect of amine oxidase on the blood pressure of hypertensive rats, a suspension of this enzyme from hog kidney was prepared according to Kohn (6). The intramuscular injection of this enzyme suspension resulted in no significant lowering of blood pressure. The ineffectiveness of these injections was probably due to the fact that the enzyme did not come in contact with the blood stream so as to catalyze the oxidation of the pressor amines contained therein. During the course of this work an extract of hog kidney was made according to Page (7), as it might contain amine oxidase. It was found that this extract had no amine oxidase activity whatsoever. The extract also caused variable and not very significant lowering of blood pressure on intramuscular injection into hypertensive rats. Grollman's extract (8) of hog kidney was also examined for the presence of amine oxidase, with negative results.

Effect of o-cresolindophenol. By analogy with *in vitro* experiments, two factors are necessary for the oxidation of amines in the body. One is amine oxidase and the other is oxygen. The content of amine oxidase in the kidney cortex was found equal in hypertensive and non-hypertensive human beings in experiments with freshly autopsied material. This was determined by measuring the oxygen uptake of a mixture of macerated kidney cortex in M/15 phosphate buffer (pH 7.5) and tyramine in a Barcroft-Warburg respirometer. The average oxygen uptake in cu. mm. per ten minutes per gram of kidney cortex, using 5 mg. tyramine in a total volume of 4 cc., was 10.7 cu. mm. for the normal kidney and 10.5 cu. mm. for the hypertensive kidney after subtraction of the oxygen uptake due to the macerated kidney itself. Since the ischemic kidney suffers from an oxygen depletion, the possibility of circumventing this difficulty by supplying it an additional hydrogen acceptor suggested itself. Philpot (9) has shown that o-cresolindophenol can accept hydrogen from amines in the presence of amine oxidase. The following equations show the reactions involved:



o-cresolindophenol leuco base

$$R{-}CH{=}NH + H_2O \longrightarrow RCHO + NH_3$$

$$\text{leuco base} + \tfrac{1}{2}\,O_2 \longrightarrow \text{o-cresolindophenol} + H_2O \qquad (4)$$

By injecting o-cresolindophenol it was thought possible to destroy the pressor amines formed in the kidney of hypertensive animals. Intramuscular injection of 10 mg. of the substance in aqueous solution produced a drop of 30 to 40 mm. blood pressure in 3 out of 6 hypertensive rats. Injections of the same amounts into 6 normal rats had no effect on the blood pressure of these animals.

SUMMARY

1. The destructive oxidation of pressor amines in the kidney requires the enzyme amine oxidase and oxygen or another hydrogen acceptor.

2. o-Cresolindophenol displays a variable effect on the reduction of blood pressure of hypertensive rats. Due to its function as a hydrogen acceptor, it may take the place of oxygen in the ischemic kidney.

3. We can confirm the impossibility of separating the enzyme from the cellular structure of the kidney and other tissues.

We wish to express our appreciation to Dr. Harry Sobotka for his valuable advice during the course of this work.

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SARCOIDOSIS

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Boeck's sarcoid has been considered more or less as a disease primarily of interest to the dermatologist. Stainsby (1) in "The Textbook of Medicine by American Authors," edited by Cecil, as late as 1938 (fourth edition) did not mention any systemic manifestations of the disease and considered it as a dermatologic entity devoting a quarter of a page to its description. Boeck's sarcoid, however, is a systemic disease and one of increasing interest to the clinician. Most American investigators have reported that the disease occurred primarily among Negroes, Puerto Ricans and Indians. As reports of the disease become more common investigators found it as frequent among the white population. Among the thirteen cases seen since 1934 at The Mount Sinai Hospital wards and Out-Patient Department Clinic, seven were white, three were Puerto Ricans, and three were Negroes. The disease is chronic and benign in nature occurring mostly in young adults. The prognosis is good. The patient most often does not appear sick. He may come to the physician to ask the cause of the peculiar eruptions he has noticed or he may seek the services of an opthalmologist in curing an eye disease. On the other hand the discovery may be purely accidental in the course of an x-ray examination to rule out tuberculosis.

In 1899 Boeck (2) described a new clinical picture under the name of multiple benign sarcoid of the skin, the essential morphologic feature of which was a group of nodular lesions. In 1915 Kuznitzky and Bittorf (3) reported the first case of systemic sarcoidosis. Since then the disease has been reported in widely variable clinical forms. The condition in a majority of cases is of relatively long duration. It is possible that cases in which the condition is of short duration have been overlooked or wrongly diagnosed in the past. No organ is immune from attack. It reveals itself in cutaneous, osseous, ocular, lymphatic and respiratory manifestations. It is therefore usually confused with tuberculosis, syphilis and leprosy. Diagnosis is facilitated by the presence of skin lesions. However, in many instances systemic complaints or glandular enlargements antedate the onset of the dermatoses. Thus, it may be confused clinically with Hodgkin's disease, lymphosarcoma, and leukemia. Therefore, the correct diagnosis is usually made by exclusion and biopsy.

Etiology: At present, etiology is still a moot and perplexing problem. Most pathologists believe that the disease is tuberculous in origin. However this opinion is not generally shared by clinicians. Etiologic studies have been directed toward the demonstrations of tubercle bacilli in the lesions. The use of various animals, such as rabbits and guinea pigs, have given disappointing results. Cultural studies have resulted in inconstant observations of a variety of organisms. The pathologic reaction is not specific for any group of bacteria.

Similar epithelioid reactions can be elicited by tubercle bacilli, fungi or even inert substances like phosphatide or wax derivatives of tubercle bacilli (4, 5). Similarity of the bony and facial lesions to those of leprosy have been pointed out by other observers. According to Filho (6) the entire sarcoid syndrome may be found in leprosy, including the skin lesions, lymphadenopathy, bone changes, histology and energy to tuberculin. Constant observation of eosinophiles in the blood point to an allergic state. Williams and Nickerson (7) prepared an antigen from the sarcoid tissue with which they injected the patient intradermally. The presence of sarcoidosis was indicated by the appearance of an erythematous patch in four of the cases within twenty-four hours. Mellon and Beinhauer (8) think that sarcoidosis is caused by a rough form of tubercle bacilli with lowered virulence. They reported that they were able to recover from one Negro patient with non-caseating tuberculosis a "partially acid-fast actinomycotic organism" and from another patient "a diptheroid bacillus containing acid-fast granules." They considered both these types to be an integral part in the life cycle of a tubercle bacillus. On the other hand Schwarzschild (9), repeating Mellon and Bernhauer's work came to the conclusion that sarcoidosis was not caused by the tubercle bacillus. Other investigators, pointing to the neutropenia and leucopenia, very often found in the disease, believe a virus causes the disease.

Pathology: This disease manifests itself as a disseminated granuloma of distinctive type. No matter where the condition manifests or localizes itself, it produces an identical type of lesion, namely, infiltrations consisting of nodules of epithelioid cells. The nodules are surrounded by scattered lymphocytes (10). Giant cells are not commonly seen.

The lesion in the skin and subcutaneous tissue is a painless small elevated nodule, violaceous in color, without itching. It ranges in size from that of a pinhead to that of a walnut. It is located primarily in the cutis, although the deeper layers of the subcutis may be involved with no surrounding erythema. Histologically it presents all the typical features of the granuloma. It is most frequently seen in the face, the upper and lower extremities.

Lymph nodes are often involved in the granuloma. The most common are the tracheo-bronchial nodes, tonsils, axilla, epitrochlear and inguinal regions. The glands are painless and as a rule do not adhere to surrounding tissues.

Osseous lesions are often discovered incidentally by x-ray examination. In occasional cases there are obvious deformities. The changes consist of areas of rarefaction which lead to circumscribed cystic cavities. They are most frequently seen in the extremities, particularly the fingers, and orbit. The histology is the same as that found elsewhere.

Obstinate conjunctivitis and iritis often are part of the clinical syndrome (uveoparotitis).

Lung markings in the x-ray reveal scattered miliary spots giving a marbled appearance which some consider pathognomonic for sarcoidosis. These as a rule are not demonstrable by percussion and auscultation.

Other viscera such as the liver, spleen or kidney may be involved, but rarely cause symptoms. Cases have been reported of heart failure due to myocardial involvement.

The blood findings reveal an increase of eosinophiles with a tendency toward neutropenia and leucopenia. Hyperglobulinemia has also been reported (11).

Most cases of sarcoidosis are negative to tuberculin tests.

CASE REPORT

History (O.P.D. 40-6503; Adm. 467870). The patient, a twenty-six year old married woman, white, an American of Italian extraction was first seen in the Out-Patient Department Medical Clinic in November, 1940, having come for a periodic examination after her discharge from a hospital in Pennsylvania. She was well until five years before admission to the clinic when she began to cough and feel tired. She had been told by her physician that she had heart disease. Ten months previously she had given birth after having ankle edema, hypertension, headaches and albuminuria during the last three months of her pregnancy. At home she soon noticed the presence of foot and ankle edema which was more marked at night, disappearing by morning. Eight months previously she had had an illness consisting of general aches in the joints and extremities, and palpitation with fever. During hospitalization at that time, in Pennsylvania, x-ray examination of the chest showed bilateral paramediastinal intrathoracic lymphadenopathy but a tuberculin test was negative. She was discharged and was told to have a frequent check-up. Four months before admission to this hospital she returned to this city and has felt fairly well since that time excepting for an infrequent cough and a little breathlessness upon moderate exertion. There have been no further symptoms.

Examination: No abnormality was noted in the head or neck. The lungs were free of râles and other abnormal findings. There were signs of a mitral stenosis and insufficiency but no evidence of decompensation. Blood pressure 115 systolic and 80 diastolic.

There was no enlargement of the spleen or liver, no tenderness, no clubbing of the fingers or other abnormal findings.

The clinical impression after the first examination was: 1) Mitral stenosis; 2) inactive rheumatic heart disease; 3) tuberculosis (?); 4) Boeck's sarcoid (?).

Course. Roentgenologic examination of the chest was repeated and revealed there was no evidence of disease in the lung parenchyma or pleura. There was considerable bilateral para-mediastinal adenopathy with sharply defined borders. X-ray examination of the bones including the hands were negative. The tuberculin test was repeatedly negative. The blood count was normal. This finding strengthened the conviction that we were dealing with a case of Boeck's sarcoid. The patient was followed and at the appearance of a lymph node at the supraclavicular region was admitted to the hospital for biopsy. The diagnosis was Boeck's sarcoid.

On subsequent examination (follow-up) she has continued feeling well, and has had no other lymphatic changes.

SUMMARY

1. Boeck's sarcoid is probably not so uncommon as it is supposed to be and is a constitutional disease which occasionally has skin manifestation.

2. Boeck's sarcoid frequently simulates tuberculosis or Hodgkin's disease but has a much more benign prognosis.

3. Its chief features are enlargements of lymph nodes, a characteristic cutaneous nodular eruption and focal lesions in the bones. Other features are miliary

lesions in various viscera. In the lung they may cause diffuse fibrosis. Right heart failure, hyperglobulinemia have been reported in this disease.

4. It is probably as common in the white race as in the Negro.

5. The etiology is still undecided.

6. In the case presented, as in many others reported, there were no skin lesions and the diagnosis was made as a result of biopsy of an enlarged lymph node.

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HOW I CAME TO DALHOUSIE

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Although the name of The Mount Sinai Hospital in New York does not appear in the following pages, this institution indirectly played a definite role in my scientific career in America. Being a new-comer and a complete stranger in the New World, I could scarcely have made a right decision in the difficult problem which confronted me without the advice and help of three men who at one time or another have belonged to the staff of The Mount Sinai Hospital. In subsequent years, during my frequent visits to New York, I had the pleasure of meeting and establishing friendly relations with many outstanding representatives of the medical, surgical and laboratory staff of this fine institution—to mention only a few names—Drs. A. A. Berg, B. B. Crohn, F. Hollander, R. Colp, E. Libman, G. Shwartzman, A. Winkelstein and others. Almost every year at a special meeting I reported to them on the progress of the work of my laboratory at McGill University, where I have held the position of Research Professor of Physiology since 1928, when I left Dalhousie University. I always greatly appreciated their interest in and encouragement of the research work in which I and my co-workers were engaged.

It is seventeen years since I first stepped on Canadian soil. Those who have not lived through the dreadful storm of a revolution can hardly understand the great relief and the feeling of profound gratitude that were mine when my battered ship entered the quiet harbour of an "ordinary" life. It is somewhat more than pleasant recollections that I have of Dalhousie and Halifax. In this article I propose to tell the story of my coming to Dalhousie.

One beautiful July morning in 1924 I was sitting on the deck of a big transatlantic liner. Three days before my wife and I had left England, where we had spent two years since my exile from Soviet Russia. Being unable to obtain any suitable appointment in England, I had accepted the modest post of instructor in pharmacology at Washington University, St. Louis, kindly offered to me by Dr. H. S. Gasser, who at that time was working in University College, London.

Had I left Europe forever? What would our life be like in America, and what kind of people were the Americans? Was this instructorship to be the end or a new start in my scientific career? None of these nor any other questions bothered me at the time. How could they bother me? For the first time in ten years we were enjoying a spell of luxurious life free from worries and troubles. For a while I could forget the incessant tension of the war, the horror, the misery and the humiliation of the revolution.

The ocean was as calm as a river on a bright summer day. It was a delight

[1] Read by title at a meeting of the Physiology Club held at The Mount Sinai Hospital, May 14, 1942.

to look on this huge round blue expanse surmounted by an immense, light blue dome. In the very middle of this space was our liner, seemingly motionless. I do not think there were many thoughts in my mind. Its analytical capacities were temporarily lost and it was in that divine state when surrounding nature is perceived as a whole. I wished only that our liner could remain under this dome in the middle of this magic blue circle as long as possible.

Suddenly my siesta was interrupted by a steward. "There is a cable for you in the wireless department," he said. At once I came back to life. The only message which I could expect was from my son-in-law, an officer in the U. S. Army. He had not been sure whether he could meet us in New York and I hoped that he was now cabling that he was able to do so. I was counting greatly on his help, because the problem of landing in New York worried me. Of course we had quite legitimate visas from the American Consulate in London, which had been obtained after long hours of tiresome standing in the street and in the corridors of this institution, and after short but unpleasant talks with its officials. But what value have all these sheets of paper with red paper seals or without them, when one is a Russian refugee with an old Czarist passport? An immigration officer will show greater courtesy to a travelling dog or cat! As a matter of fact the beginning of our voyage was marked by a very unpleasant incident. An employee of the steamship company at Southhampton who inspected the passengers' passports refused in a very rude manner, and without any reason except that we were Russians, to allow us to embark on the boat. Only with the help of a less jaundiced and undoubtedly more intelligent American official was the matter settled quickly and satisfactorily.

Great was my surprise and even consternation when I read the following telegram: "Professor Hill recommends you professorship physiology Dalhousie University. On landing could you come Halifax for consultation? If not, when could I meet you? (signed) Dalhousie." Dalhousie University! I suddenly remembered what it all meant.

Two days before our departure from London I went to say good-bye to Professor A. V. Hill, who at that time was in charge of the Department of Physiology in University College, London, where I worked for two years after leaving Russia. He expressed regret that no position could be arranged for me in England. Sad as it was for me, I could not reproach anybody for such a state of affairs, and especially not this man who always seemed to me to be so profoundly sympathetic towards others and so exceptionally honest in his relations with them. We parted in a most friendly manner. I was almost at the outside door when I heard Hill rushing down the stairs two or three steps at a time.

"I just opened a letter," he said. "They want a physiologist at Dalhousie. Would you like me to recommend you?"

"Dalhousie?"

"Yes. Dalhousie University in Halifax, Nova Scotia."

"Nova Scotia? Where is that?"

"In Canada. Not far at all from here. In four or five days you can always come back to England," said the Englishman.

"Thank you. If you think that with my poor English I am fitted for this position, please recommend me."

On reaching home I told my wife about my conversation with Professor Hill. She paid very little attention to what I said. Her thoughts were directed towards North Carolina where our daughter was, whom we had not seen for two years. And very soon we had both completely forgotten about Dalhousie, Halifax and Nova Scotia. In the meantime presumably Professor Hill had communicated with President Mackenzie of Dalhousie University, and the President had cabled me on the liner.

I put the telegram in my pocket, sat down in my chair again, and tried to return to my state of nirvana. Alas! the beautiful dream had disappeared. I found myself again on a crowded and noisy liner, continuously vibrating to the rotations of her propellers and moving forward with irritating slowness. A red-faced gentleman, whose chair was not far from mine, was speaking to his neighbour in a thin, tiresome voice, which he modulated in that unnatural manner sometimes referred to as the "Oxford" accent.

However, I had to answer the President's telegram. The only possible way of learning something about Dalhousie University was to consult somebody in New York. It was very fortunate that one of my most distinguished former students from the University of Odessa, Dr. G. Shwartzman, was at that time in New York, where he occupied a Chair of Bacteriology in one of the medical schools. I replied to President Mackenzie that I would inform him of my decision from New York.

It seemed that the Dalhousie cablegram marked the end of our carefree and pleasant life on the liner. Next day the ship's journal reported a fresh northwest wind and a moderate sea. In ordinary language this meant that our boat rolled continuously and desperately slowly from one side to the other. It creaked and groaned, and in Maxime Labelle's words from Drummond's "Habitant,"

"An' so we all come very sick, jus' like one little pup,
"An' ev'ry tam de ship's go down, de inside she's go up."

The "moderate sea" had not yet at all moderated its unwelcome activity when a new trouble arose. The Assistant Purser, whose duty it was to attend to the second class passengers, lost my wife's and my immigration papers. I do not remember the exact name of these papers. They were of huge size and printed on both sides with questions which the U. S. Government required us to answer in the proper way. I had completed one set of these papers (and of course another set for my wife!) and emphatically denied that I was either an anarchist or a communist. I assured them that I was not a polygamist and that I did not intend to overthrow the United States Government. I do not think there was a question as to whether I was a member of a racketeering gang, but I had to declare if I was mentally sane, which I did.

The Assistant Purser was rather a romantic young man. He was far more interested in two girls, who according to rumour were English actresses, than in my immigration papers. Whenever the Assistant Purser entered the dining

room or saloon, he stood for a while like a penguin, his nose in the air, slowly moving his head to right and to left, trying to locate the girls.

I sat down to fill these papers again. My wife, like so many women, did not realize the importance of this formality and preferred to stay on deck chatting with the new acquaintances whom she had met on the boat. So I was left alone with a double job. I had not yet quite got over the effects of the north-west wind. Oh! how indignant I was at the romantic adventures of the Purser, whom I held responsible for my misfortune. I put down on the paper as before all the things which the United States Government wanted to know about us. Then I came to the query: "Complexion?" My complexion? Probably at that moment I was pale, but I was not sure what complexion I have in happier circumstances. After long deliberation, and being afraid of disappointing the immigration officer, I wrote down, "Complexion—all right." Thoughts about my complexion exhausted me completely. What kind of complexion had my wife? I wrote, "Complexion—pink," to which she objected very much afterwards. But I honestly thought that it would help her gain admittance to the United States.

At last we arrived in New York. My son-in-law and Dr. Shwartzman met us. I told Dr. Shwartzman about Dalhousie. He considered the offer a very good one, but did not know enough about the University to advise me to accept the post. Accordingly he invited to the hotel where we were staying the late Dr. Louis Gross, whom I had met a year before in London. Dr. Gross arrived immediately. After a short consultation the two young men took me to see Dr. E. Libman, a famous New York clinician. The sincere interest of this man in the fate of a complete stranger, as I was to him then, touched me greatly. His vivid mind worked with extreme quickness. In a few minutes he outlined a plan which I was to follow, and which I actually did follow. Since a chair in physiology and not an instructorship in pharmacology was what I actually wanted in coming to America, I had to consider the Dalhousie offer with all seriousness. I must go to Halifax immediately and find out personally about the conditions of work there. If they were suitable, I was to accept the offer. But I must not forget that I was under certain obligations to Washington University. In the event of my acceptance of the Dalhousie appointment, the President of Dalhousie, and not I myself, would have to negotiate for my release from my agreement with Washington University. A few days later, after certain passport and other formalities had been settled, I warmly shook the hand of my friend Dr. Shwartzman at the Grand Central Terminal and thanked him for his inexhaustible kindness.

I had a strange feeling of amazement mixed with a sense of grave responsibility concerning all that was happening. Things were not so simple as they seemed, and although it might seem a lucky chance for me to exchange the instructorship at St. Louis for a full professorship at Dalhousie, I had been told by my friends in England and believed myself that the pharmacological laboratory at Washington University would be the first step in my scientific career

in the United States. I must confess that Canada had never entered into my considerations. I now fully realized that the acceptance of the Dalhousie offer would change altogether the course of my scientific and personal life and the future of my family. Had we not had enough of such changes in the last ten years?

As I looked from the train window on this American land, one thing impressed me. A European is accustomed to think of America as a country of steel and concrete, but this is true of the big cities only. On the outskirts one already begins to see wooden buildings, and between the cities it is difficult to find a house that is not of wood. The long trip was rather uneventful, the salient feature being the terrific heat, especially between New York and Boston. Never in my life before had I suffered so much from thirst. I did not know then that there was iced water in the car! Great was my relief when the next morning after an uncomfortable night (my first night in a Pullman car!) I had breakfast in a quiet, clean restaurant at McAdam Junction. This was Canada! The morning was cool. Spruce, pines and birches reminded me of my own country. A small lake reflected the white clouds which moved high up in the pale blue sky. How nice and friendly everybody was on this fresh summer morning! And what a contrast it was to the noise and heat of New York! Then followed an endless and tiresome journey to Halifax, where we did not arrive till eleven at night.

The old wooden station building was poorly lighted and humble. It was too dark to see the city. However, I noticed that there was some kind of celebration going on. Crowds were walking in the streets and among them many officers in full military uniforms. Thin threads of light marked the contours of the battleships in the harbour.[2] A taxi took me to the Halifax hotel. It was the shortest and most expensive drive that I ever had. Hardly had I taken my seat in the old, shaky Ford than we arrived at our destination, and the driver charged me one dollar. With great difficulty I found a spare room in the hotel, so overcrowded was it.

Next morning was not cheerful. Rain poured and heavy grey clouds hung over the city. A wooden building with narrow windows across the street was soaked with water and looked ugly. I was waiting for President Mackenzie in the lobby and easily recognised him in a tall, dignified man who approached the counter. We introduced ourselves to one another. He took me in his car to his office at Studley. Unhurriedly he explained to me the position of Nova Scotia in the Dominion and the place which Dalhousie University occupied in the Maritime Provinces. Then he spoke about the vacant Chair of Physiology, which he again offered to me. I recollect this conversation with great satis-

[2] 1924 marked the one hundred and seventy-fifth anniversary of the founding of Halifax, and it was celebrated during the week of August 5 by a street fair, a pageant representing the landing of Cornwallis, and so on. There were two British warships in the harbour, H.M.S. "Hood" and H.M.S. "Repulse", and one Australian warship, H.M.S. "Adelaide." On August 7 there was an official reception on board the "Hood," with which the festival was concluded. I arrived in Halifax on the night of August 7.

faction because a feeling of understanding was reached between us so easily and quickly. President Mackenzie fully realised the importance of the Chair of Physiology in the University, and consented to the appointment of a permanent assistant—an experienced man who would help me with the teaching. Besides this I was promised a laboratory boy and sufficient funds for additional equipment and maintenance.

The favourable impression created on me by this conversation was further increased when President Mackenzie showed me my future laboratory in the Medical Science Building. Frankly I did not expect to see in a small University a perfect modern laboratory building. Five rooms were allotted to the Department of Physiology. The equipment was rather poor, but since money was promised this did not worry me. In the medical building I met Dr. W. H. Hattie, Dean of the Medical Faculty, Dr. E. G. Young, Professor of Biochemistry, Dr. O. S. Gibbs, the newly appointed Professor of Pharmacology, and in the recently completed Health Centre, where the President took me, Dr. A. G. Nicholls, Professor of Pathology. The friendship of all these men I afterwards appreciated very much.

The difficulties of this day were not yet over for me. The lunch in the Halifax Club, to which President Mackenzie invited me, was quite an unusual affair. It happened that the very day I came to Halifax, the newly appointed President of King's College, the Rev. Mr. Moor, had arrived. A lunch was given jointly for both of us to introduce us to Archbishop Worrell, and to Mr. G. Campbell and Mr. G. F. Pearson, Chairman and Vice-Chairman respectively of the Board of Governors of Dalhousie University. It was pointed out to me that the lunch would be a Nova Scotian one. Indeed, for the first time in my life I was served with fish chowder. Since I for my part had already almost decided to accept the chair at Dalhousie, I ate it bravely. Then we were given some kind of fish, also new to me, but delicious and fresh as only fish in Halifax can be. The dessert gave me an opportunity for revenge. Blueberry pie was served, and I was asked whether I knew this kind of berry. Did I know blueberries! According to the Russian Encyclopedia the name of Babkin appears about the thirteenth century in the district of Novgorod in Northwest Russia. This is a real blueberry country. Not only I from my childhood but undoubtedly all the Babkins in past centuries ate blueberry pies!

In spite of my boasting about the blueberries I passed my examination at this luncheon satisfactorily, as the development of events showed me later.

After lunch the rain stopped and Mr. Pearson took us for a drive to the Ashburn Golf Club, from where I was brought to my hotel and left to my own devices. I stretched myself out on the bed in my room, recollecting all the conversations that had passed. I endeavoured to restore the impressions which different persons had produced on me and to guess what impression I had made on them. I considered again the alternative prospects of work at St. Louis and at Halifax. I realised that these few hours before President Mackenzie would come to see me again at 8 o'clock in the evening were of great importance for my decision.

It started to rain heavily again. Drops were forming on the windowpane. They moved down the glass zigzag, absorbing smaller drops on their way, and near the bottom formed into a little rapid stream. Rain is an unlucky omen at a wedding. Was not this the day of my wedding with Dalhousie? The monotonous movement of the rain drops probably caused me to doze, because when I got up it was already 5 o'clock.

I decided to go for a little stroll in the streets. It had stopped raining. The heavy grey clouds were partly broken, letting through more light from the still hidden sun. The harbour with its dark water looked unfriendly. The small wooden houses, some of which were unpainted and were therefore almost black from the recent rain, looked sad. There was very little traffic in the streets. What a contrast to New York and probably St. Louis! Would I have to live here forever?

I found myself on the main street of the city. Most of the buildings here were of concrete, although here and there old wooden two or three story boxes testified to the past history of the city. Street cars, modest stores and a greater number of pedestrians animated this locality. At the intersection of two streets a very tall, red-faced policeman was absorbed in a conversation with a short, stout friend. After repeated blasts from the horn of an approaching automobile, the policeman straightened himself up, looked round and indicated the direction requested by moving his arm with such vigour that it seemed as if he were throwing a ball in the face of the submissive driver. Then again he bent down to his friend and plunged into the interrupted chat.

I was now standing at the gate of a small cemetery, abandoned probably very many years ago. The growing city had surrounded it with its bustle and noise. The dark grave-stones, some of them already sunk deep in the ground, contrasted with the fresh green of the leaves and grass which were still wet. In the middle of the cemetery stood an ark with the figure of a lion on the top. I read the inscription, "Sebastopol" and below "Alma, 1855. Redan", "Weesford, 97 Reg.", "Parker, 77 Reg." This ark was probably in commemoration of two officers killed in action during the Crimean War.

Sebastopol! How many memories did this name evoke in me! My grandfather, Ivan Babkin, with the rank of colonel, and my uncle, Alexander, then a young lieutenant, participated in the Crimean campaign. The military traditions and memories of 1854-55 were very much alive in our family. One of my favourite books was a story in three volumes with numerous wood-cuts of the siege and defense of Sebastopol. Admiral Kornilov and Admiral Nakhimov were my childhood's idols. How fine it would be, I thought, to become a hero like one of them and die a glorious death! From the conversations of our elders we children gathered that the chief enemy of Russia was "perfidious Albion." Only very gradually was this impression dispelled among the Russian public, not perhaps fully until the beginning of the Great War.

I stood probably too long before the monument, because one or two passersby looked at me with curiosity. But it was something to think about! The children and grandchildren of those who fought against my own people now wanted to

accept me as their fellow member in one of the most vital institutions of their land. How little we understand the tortuous course of history, and how cruelly we are deprived of the capacity of prevision! I do not think that the Sebastopol monument directly influenced my decision concerning Dalhousie University. But the unknown path of Destiny which was revealed by the sight of it undoubtedly reminded me that there is One who knows what is good for us often better than we do ourselves.

When the same evening President Mackenzie came to the hotel to talk over the whole matter with me, my decision to accept the chair was already made.

*The Story of The Mount Sinai Hospital, of which the first three installments appeared in preceding numbers of the Journal, is offered in celebration of the Hospital's ninetieth birthday. In its present form it consists mainly of brief historic notations which to some extent reflect the "way" of medicine in New York and elsewhere, as well as the changing environment since 1852. It has been compiled by Miss Jane Benedict from Hospital records, correspondence, medical and historical literature, and interviews with those who have been both eye-witnesses of and contributors to the Hospital's progress. It is presented mainly as source material from which later a more complete history of the Hospital is to be written.**

The first three installments were devoted to a description of the founding and founders of the Jews' Hospital, the forerunner of the modern Mount Sinai; to an account of the organization of its first medical and administrative staffs, with a few notes on surgery as it was practiced then as a background.

This installment recounts events during the years of the Civil War, a period which afforded the Jews' Hospital an opportunity to participate in a national emergency. A view is given of the character of nursing care available at that time; of the current public attitude toward post-mortem examinations, and of the men who were influential in shaping the Hospital's medical tradition.

THE FORMATIVE YEARS, 1852-1872

IV

Nursing at the Jews' Hospital was neither better nor worse than in any other institution during that period. Trained nurses were unknown. Women were hired without any previous schooling in the care of the sick. They were usually uneducated and frequently slovenly. The men employed to attend male patients—for women did not take care of the men—had no better training. The minutes of the Board meeting for February 1, 1857, cast an interesting sidelight on the nursing of that early period. The Directors resolved: ". . . also to engage for the first and second wards two additional nurses so that in each ward there may be a day and night nurse, that nurses shall exclusively give all medicines to the sick, and that boxes be placed over each bed in such a way that no sick person could reach the medicine in them."

Although there were some religious sisterhoods which trained their members in the care of the sick poor, there were in the United States no nurses' training schools as we know them today.[57] The year before the opening of the Hospital, when the Crimean War broke out in Europe, Florence Nightingale was sent to Scutari to superintend the hospital barracks there. So successful were the reforms she effected, in the face of opposition and petty cavilling, that after the war a Florence Nightingale Fund of fifty thousand pounds was raised to start a training school at St. Thomas' Hospital in London. Florence Nightingale had

* Corrections, if errors of fact or interpretation are discovered, and additional information which may help to make the picture more complete, are welcome and may be addressed to the Historian of the Hospital.

[57] Sigerist, Henry E.: American Medicine, W. W. Norton Co., 1934.

received her training at a school for deaconesses founded by a German pastor and his wife.[58] In 1860, five years after the Jews' Hospital in New York had opened its doors, the training school at St. Thomas' Hospital in London started its first course with fifteen probationers. But it took thirteen years before the first training school in the United States was founded at Bellevue Hospital, and it was not until eight years later, in 1881, that Mount Sinai incorporated its school.

In its first years the work of the Hospital was sectarian. Two days before the Hospital was opened for the reception of patients the Board passed a resolution "... that the Visiting Committee be instructed not to receive any patients other than Jews except in cases of accident, until further notice of the Board." The same religious principles which set the regulations for the Visiting Committee also controlled the matter of post-mortem examinations. On December 5 of that first year of service, Dr. Blumenthal asked permission of the Board to perform a post-mortem examination in order to justify his diagnosis concerning the cause of death. Permission was granted, but only by a margin of one vote.[59] As the result of the controversy which followed this decision among the Board members, a letter was sent to Rev. N. M. Adler, Chief Rabbi of All Jews in the British Empire, asking his advice on the subject. The answer was that autopsies were desecration of the dead with only two exceptions: when someone is accused of murder and an autopsy may prove that the deceased died a natural death; and when the cause of the disease is unknown and other patients exhibit symptoms similar to those of the deceased.[60] This opinion was accepted as final, but nevertheless permission to make post-mortem studies was granted usually by a close vote of the Board. In the years between 1855 and 1870 the minutes show only one occasion when such permission was actually refused.

As the Hospital grew, its activities necessarily spread beyond its immediate building. Dr. Blumenthal's report covering 1856 explains this expansion: "At first its (the Hospital's) charities extended only to its inmates, only special cases receiving care outside the walls of the Institution. These out-door patients were also attended to if able to come and present themselves once or twice weekly; and in this direction, the Hospital's usefulness has now extended so far, that it deserves to be considered one of its most important branches particularly as the German dispensaries, to which many of our poor resort, are down town, too far to be available to the poor in the upper part of the City." Many years elapsed before an Out-Patient Department was established, as a distinct unit.

Continuing his report, Dr. Blumenthal pointed out that of the two hundred and fifty patients admitted in 1858, fifty-four were "pedlers"—"... a fact ascribable to so many immigrants being cast upon our hospitable shores, without profession or trade. On the female side, forty-nine are domestics, a class that in view of the many hardships to which its members are exposed, is deservedly

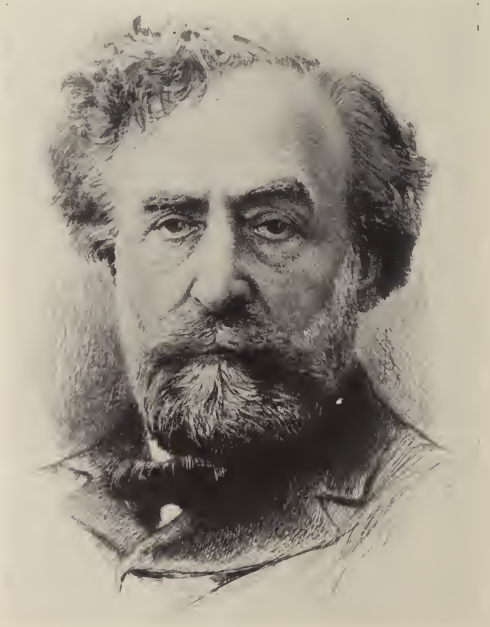
[58] Garrison, Fielding H.: History of Medicine, W. B. Saunders Co., 1924.

[59] Minutes of Board of Directors' Meetings, Jews' Hospital, December 5, 1855.

[60] Letter from Rabbi N. Adler, Reprinted in The Occident, Isaac Lesser, Editor, June, 1856.

considered as highly worthy of the benefits the Hospital can offer. Many of this class are very young, and have in their homes enjoyed comparative comforts, having, perhaps, never before been separated from their natural protectors, but are here coerced into service as a means of subsistence."

In 1859 the Board turned its attention to the reorganization of the Medical Staff. The position of Resident and Attending Physician was abolished. Instead, three Attending Physicians were appointed, and the position of House



Dr. Abraham Jacobi

Physician and Surgeon created. One of the Attending Physicians thus appointed was Abraham Jacobi, who continued in close association with the Hospital from the year of his appointment in 1860 until his death in 1919. During these years he witnessed the tremendous strides made by American medicine with the discovery of antisepsis and asepsis; the progress in surgery; the advance of preventive medicine; and the development of his own special field of pediatrics. He was an active participant in the fight for improved civic conditions in New York, and a most enthusiastic citizen of his adopted country.

Abraham Jacobi was born in Germany in 1830, and came to the United States in 1853, the year after Sampson Simson founded the Hospital. At twenty-three Jacobi had already seen much of the dramatic in life. He came of poor Jewish parents, and his education was gained at the cost of considerable privation. In the manner of European students of that day, he went from one University to another, from Greifswald to Göttingen and from there to the University of Bonn, from which he graduated in 1851. He first studied Oriental languages, but soon was attracted to medicine through his interest in anatomy and physiology. Meanwhile the Revolution of 1848 broke out, and the young student was drawn into the struggle. Therefore, when he went to Berlin to appear for his examinations, he was seized by the Prussian authorities and imprisoned for a year and a half in the fortress at Cologne. Finally, acquitted of the charge of treason, he was convicted of lèse majesté and sent to Minden. He served only six months of his sentence, for having gained the friendship of the jailer, he made his escape to Hamburg where he boarded a ship for England. From England he embarked on a forty-three day voyage to the United states, landed in Boston and from there made his way to New York.[61] He set up offices at 20 Howard street and in the first year of practise earned nine hundred seventy-three dollars and twenty-five cents by charging twenty-five cents for office visits, fifty cents for house calls and five to ten dollars for obstetrical cases. In the first year ". . . he found his workshop and temple—the New York Academy of Medicine." Its presiding genius was Valentine Mott ". . . easily the dominating Asclepiad of the generation."[62] Dr. Jacobi was admitted to fellowship in the Academy in 1857 and in the same year became a lecturer on pediatrics at the College of Physicians and Surgeons.[63]

One year before Dr. Jacobi was appointed to the Staff of the Jews' Hospital, he had written in collaboration with Emil Noeggerath a book, *Contributions to Midwifery and Diseases of Women and Children*, which was published at a cost of eight hundred dollars to the authors. The unbought copies were a drag on the publisher, and the authors bought the entire edition, but having no space to store it, sold all the copies for waste paper. Despite its conspicuous lack of success, the book had distinct value and was one of the first efforts in that field.[64] Jacobi adopted the United States as his home with a devotion which many years later, in 1903, was to make him reject the coveted Chair of Pediatrics at the University of Berlin because of his preference for this country.[65] His acceptance of the Chair of Pediatrics at the College of Physicians and Surgeons marked the beginning of "clinical and scientific pediatrics in this country."[66] By 1860 he held the special Chair of Diseases of Children in the New York Medical College. Here, two years later, he established a pediatric clinic—the first in this country.

[61] Garrison, Fielding H.: Dr. Abraham Jacobi, Reprint Science N. S., Vol. 50, No. 1283, 1919.

[62] Medical Life, Jacobi Number, Victor Robinson, Vol. 25, No. 5, 1928.

[63] See footnote 61.

[64] See footnote 62.

[65] Knopf, Dr. S. Adolphus: Abraham Jacobi, In Memoriam, Privately printed, 1919.

[66] See footnote 61.

The New York Medical College, however, did not survive the Civil War, since many of its students were Southerners who left New York during that period. In 1865 he accepted the clinical chair in the Medical Department of the University of New York, and in 1870 was appointed Clinical Professor of Pediatrics.

According to the rules laid down with the reorganization of the Medical Staff of the Jews' Hospital, the House Physician and Surgeon must be a medical graduate, to be appointed for one year by the Board of Directors after having been examined by the Medical Board. The young man thus appointed was Dr. Seligman Teller who served in that capacity for twelve years. His salary for the first year of his service was one hundred and fifty dollars, and later was gradually increased to four hundred dollars. When the young doctor married, in 1867, the Board of Directors rented one floor of a building adjacent to the Hospital for the sum of three hundred dollars a year as a home for the doctor and his bride. Dr. Teller contributed one hundred dollars to the rental. It is recalled that Mrs. Teller used to visit the patients daily and that one day, feeling particularly sorry for a young boy, she went home and baked him a cake.[67] What this did to Hospital discipline is not on record. Dr. Teller died in 1885. Another German-American, Dr. Ernst Krackowitzer who like Jacobi was a political exile from Germany, was among the early appointees of the Hospital. He was associated with Dr. Jacobi and took the place of Dr. Thomas Markoe as Attending Surgeon. He was a well trained surgeon and pathologist who later established the German (now Lenox Hill) Hospital in New York. He died of typhoid fever in 1875, and Dr. Jacobi, his intimate friend and great admirer, delivered his eulogy at the New York Academy of Medicine.[68]

The reorganization of the Medical Staff was taking place at the time the threat of civil war was hanging over the country. When the Civil War broke out there was, at first, some talk of New York remaining a free and neutral city. That idea was soon dispelled, however, and instead New York became the base for Union supplies. Moreover, on April 19, 1861, New York voted one million dollars for the defense of the Union. On the same day the Seventh Regiment, with nine hundred and ninety-nine men, marched off to Washington. On April 20, one hundred thousand people expressed their wholehearted support of the Union at a mass meeting in Union Square. Eighty-seven Vice-Presidents were elected, one of whom was Joseph Seligman, a Director of the Jews' Hospital in that year. A Union Defense Committee was organized on April 22 and continued to function until April 20, 1862. During that year it raised and gave to soldiers' widows and orphans over one million dollars. In the first year of the war, a circular addressed to ". . . the women of New York and especially to those already engaged in preparing against the time of wounds and sickness in the army," urged that a system of caring for the sick and wounded be organized. The Woman's Central Association for Relief was formed, and out of their work grew the United States Sanitary Commission.

[67] Interview with Miss Lillie Guinzburg, niece of Dr. S. Teller, June 30, 1938.

[68] See footnote 62.

Three days after the mass meeting of April 20, 1861, the Directors of the Jews' Hospital passed a resolution ". . . that the Board of Directors tender to the State authorities a ward in this Hospital for the accommodation of such soldiers who may be wounded in the service of the United States." The minutes of the Directors' meeting for June 18, 1862, indicate that forty-eight beds were bought for the soldiers as well as other supplies in appropriate quantities. Extra employees were hired, and Lewis May and L. M. Morrison were added to the Board of Directors for the period during which the soldiers remained in the Hospital. Rules for the admission of soldiers excluded those afflicted with contagious diseases, and permitted the acceptance of only ten typhoid fever cases. Apparently ten such cases were all that could be accommodated on a separate ward. The minutes of September 7, 1862, show that a special book was to be kept for donations to the soldiers and that on September 21, twenty-one more beds were provided for soldiers, bringing the total number of beds available for them up to sixty.

In 1862 the Draft Riots occurred in New York and the Jews' Hospital, in addition to the care it gave to wounded soldiers, also administered aid to some of the victims of the riots. During this uprising, which occurred when it was announced that a draft was to be put into effect, rioters broke into the Provost Marshal's office on Twenty-eighth Street, the street on which the Hospital was located. The Colored Orphan Asylum on Fortieth Street was burned to the ground, fortunately after the frightened children had been hustled out through a rear door.[69]

In 1864 a fair was held in buildings on Fourteenth Street and Union Square in order to raise money for the United States Sanitary Commission and it yielded over one million dollars. On June 8 of that year the minutes of the Directors' meeting show that Dr. McDougall, Medical Director of the United States Army for the Department of the East, inquired whether soldiers might again be cared for at the Jews' Hospital. The reply voted by the Board was that fifty soldiers could be accepted, subject to the rules concerning contagious diseases.

During the critical years of the Civil War the excellent work of the Jews' Hospital made it still more an integral part of the City. This work, in part, effected a change which influenced the future of the Hospital. In caring for soldiers irrespective of their Jewish or non-Jewish origin, in arranging for visits by ministers of various denominations to these soldiers, the Directors were preparing the gound for the non-sectarian policy which has distinguished the Hospital ever since. Exceptions had been made earlier to the older and now discarded rule laid down in 1855, ". . . that the Visiting Committee be instructed not to receive any patients other than Jews." Accident cases of all nationalities and religions had been accepted since the first day of the Hospital's existence. But the national crisis led to the Board's realization of the necessity of rising above sectarianism, and of brushing it aside completely.

Men active in Hospital affairs wholeheartedly embraced the cause of the Union

[69] Meyer, Alfred: Recollections of Old Mount Sinai Days. J. Mt. Sinai Hosp. Vol. 3, No. 6, 1937.

in those years. In July of 1861, Dr. Israel Moses resigned from the Staff in order to join the Army.[70] Joseph Seligman, elected to the Board of Directors in 1855, was often called to Washington to consult with President Lincoln on financial matters.[71] Because of his increasing responsibilities, he found it necessary to resign from the Hospital Board in 1862. Rev. Samuel M. Isaacs, who had helped to found the Hospital and had served on its Board until 1857, had continued to display his interest by visiting the patients regularly in his capacity of rabbi. During the Civil War, Rev. Isaacs was an ardent supporter of

Dr. Israel Moses

the Union and as editor of the *Jewish Messenger* was particularly articulate in championing its cause. His straightforwardness lost him many Southern subscribers and he was well aware of the results of his editorial policy when he wrote, "... we want subscribers for without them we cannot publish a paper and Judaism needs an organ ... but we want much more truth and loyalty, and for them we are ready, if we must, to sacrifice all other considerations."[72]

[70] Minutes of Board of Directors' Meetings, Jews' Hospital, July 7, 1861.
[71] Narkens, Isaac: Lincoln and the Jews. Pub. American History Society, No. 17.
[72] Editorial: Jewish Messenger, January 6, 1882.

On April 21, 1865, Abraham Lincoln's funeral cortège started from Washington and for several days his body lay in state in New York's City Hall, where thousands came to do it reverence. Rev. Isaacs read the Scriptures at the funeral.[73]

The next installment will cover some important transitions in the Hospital's history: the adoption of the name of The Mount Sinai Hospital and the preparations to erect a new and larger building; the part played by the Hospital in the cholera epidemic; the Boyne Day riots; the "frightful accident" (in an adjacent factory); and the final decision to move to new quarters, thus marking the end of the "Formative Years" and completing the first phase of Mount Sinai's history.

[73] Interview with Miss Miriam Isaacs, daughter of Rev. S. M. Isaacs, June 7, 1938.

HISTORICAL EXHIBIT, COMMEMORATING THE NINETIETH ANNIVERSARY OF THE FOUNDING OF THE MOUNT SINAI HOSPITAL

The idea of celebrating the anniversary of the founding, in 1852, of the Jews' Hospital was haled with enthusiasm and a keen spirit of coöperation. Banquets and speeches and formal occasions are the conventional means for demonstrating fidelity and respect for such an occasion. An Historical Exhibit which would by graphic means illustrate the progress and development of the physical, social and scientific growth of such an institution is a rather novel suggestion. The "Committee on Medical Education," under the auspices of the Directors of the Hospital undertook such a venture in the hope of recalling and recreating the spirit of the greater events that have dotted the path of progress of this institution.

The large hall in the Main Administration Building divides itself into five larger spaces, the walls of which serve naturally as decorative panels. The ninety years of progress are unevenly divided into decades, each panel fitted with a placard and an associated showcase, both of these serving to illustrate steps in the development, as also to portray individuals and the personal touches such as characterized a particular decade or decades.

In the center of the floor space are grouped six large, well illuminated show cases, devoted to more personal highlights in the lives and achievements of some of the men who have helped make the history of the institution. Statuettes of some of the greater individuals, decorative graphs, tables of progress, and a large (but only very partial) display of individual contemporary scientific achievements of the medical staff help to round out in a brief manner, the present day activities, and accomplishments of an alert, modern foundation.

Several of the outstanding features of the Exhibit deserve special mention. At the head of the large marble stairway that approaches the exhibit are two rather fascinating floor cases. In case "A" are shown striking photographs of Sampson Simson and of the Rev. Samuel M. Isaacs of whose minds and through whose efforts the institution of the Jews' Hospital was born. The original case-history book of early admissions to the primitive wards is open to Page One. In a fine Spencerian handscript, the clinical histories of the first cases were inscribed by the clerk. As a sectarian institution characteristic of that period the first cases admitted were all of the Jewish religion. An analysis of the first hundred cases gives a good survey of the nationalities of origin of the Hebrew population in this municipality in the early fifties. Eighty-three were of German extraction, ten were Poles, five were Russian, and two were Moroccans. The public wards of the institution, though founded and supported by Sephardic Jews, hospitably provided beds for the less prosperous and more recent immigrant classes from the Europe of 1848, economically distracted by revolutions and by social discord.

An adjoining show-case is devoted to the life and letters of the first acting

surgeon on the staff of the new Hospital, Dr. Israel Moses. Here was a fascinating man, too little recognized by his associates in his day and time, but well greeted and praised by his government. He operated upon the first surgical cases in the Jews' Hospital from 1852 until the outbreak of the Civil War. His

FIG. 1. Panel I. For the printed material on the central placard see addendum

services to our nation as Surgeon in the Mexican War, as Lieut. Colonel of Infantry in 1861 and 1862, as Surgeon again with the "Army of the Cumberland" through the latter years of that bitter strife, mark him as an outstanding personality, gracious in his radiant services to his nation, and as a credit and star

to the institution from which he emanates. The beautiful and touching letters to his family, his personal sketch books and album as displayed in the Exhibit, give an excellent picture of his personality and activities.

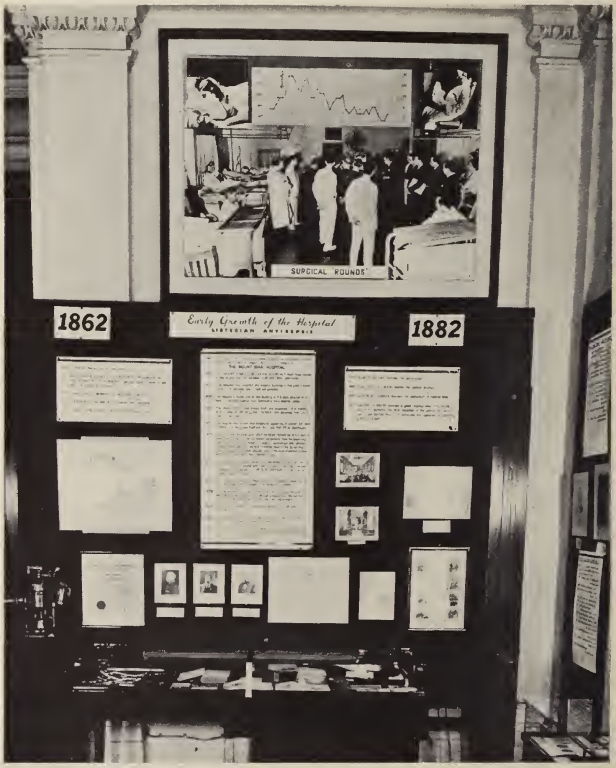


FIG. 2. Panel II. For the printed material on the central placard see addendum

The first wall panel (fig. 1) is designated "Founding of the Hospital," a period of clinical medicine, 1852–1862. An attempt to recapture the spirit of the times is made. The saddle-bag of a practitioner of the times is shown; early surgical instruments in the possession of Dr. Valentine Mott; contemporary and primitive colonic apparatus in use by the United States Army at that time; the axil-

lary thermometer and some instruments used by Dr. Abraham Jacobi in his earliest years of practice; finally a field chest of medicaments and supplies picked up on the Battlefield of Bull Run, a gracious loan from the New York Academy of Medicine, recaptures the patriotic spirit of the civil strife.

Photographs of the contemporary hospitals of early New York, Niblo's Garden, the Crystal Palace, the Incorporation Papers of the first Jews' Hospital decorate the panel. An interesting "Fee Bill" (borrowed from the Cleveland Academy of Medicine) with its startling array of fees for treatment of diseases, for obstetrical deliveries, for reducing hernias, for mileage on distant visits, recreates the atmosphere of the 'fifties and 'sixties.

FIG. 3. Lister spray of carbolic acid (loan from Dr. Dittrick, Cleveland Academy of Medicine)

Panel II (fig. 2) illustrates the "Early Growth of the Hospital," the period of Listerian antisepsis, 1862 to 1882. An actual Lister Carbolic Spray (fig. 3), standing on a pedestal characterizes the period. The first book published by a member of the attending staff, Dr. Alfred L. Loomis is displayed, as are also the earliest reprints, many of them outstanding and brilliant scientific contributions by such men as Jacobi, Barney Sachs, Lustgarten, John A. Wyeth, Koller, Koplik and Mundé.

The hospital has moved to its new quarters at Sixty-seventh street. It is now, in conformity with the changing times, a non-sectarian institution. A topographical map of the hospital on Lexington Avenue locates it as surrounded by numerous other public institutions that seemed to spring up in that area

of the extending city. The embossed invitations to the opening of the newer buildings, the Grand Charity Fair in 1870, the Joint Bazaar from Frank Leslie's Illustrated Paper, serve to reproduce the spirit and energy of the prime-movers in that expanding community.

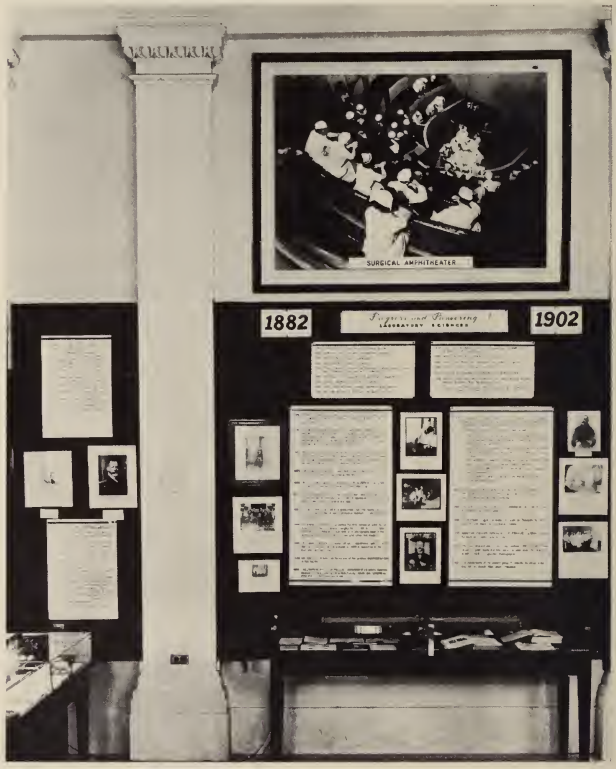


Fig. 4. Panel III. For the printed material on the two large placards see addendum

"Progress and Pioneering," the period of development of the Laboratory Sciences (1882–1902) is housed in Panel space III (fig. 4). Here is shown the discovery of local anesthesia (Cocaine) by Carl Koller in his first reprint; a series of Koplikiana, his student notebooks, the early diagnostic "spots" in measles,

reprint on "Sterilization of Milk" and a beautiful photograph of that illustrious pediatrician.

Arpad G. Gerster, revered and respected by all his contemporaries, illustrates the introduction of newer surgical methods into Mount Sinai. His discarded instrument case (fig. 5), carried around the waist, dusty and crumbling, is flanked by "Rules of Aseptic and Antiseptic Surgery" as noting the inexorable change to the newer methods.

The spirit of Welch has infiltrated the building; the new scientific laboratory begins as "a hole in the wall." Drs. Mandlebaum and Elsberg are seated at a

FIG. 5. Pre-Listerian instrument case, strapped around waist and carried handily for easy access. Sterilization of these instruments was unknown

microscope in a room not much larger than a big closet; the aura of the coming productive period of research in this institution already pervades the atmosphere.

Panel IV (fig. 6) illustrated "The Maturing Hospital," the period of clinical and laboratory research, 1902–1912. The crude instruments devised out of gas-pipe by the enterprising Dr. Sidney Yankauer, "that mechanical genius master of ingenuity," are demonstrated (fig. 7). The first radiographs taken by Dr. Eugene H. Eising utilizing the foot of an Egyptian mummy (fig. 8) for practice tryouts with the new x-ray machine are on display.

A Golden Period of research and of scientific achievements is illustrated by many reprints, some by our illustrious Libman in his path-breaking studies on

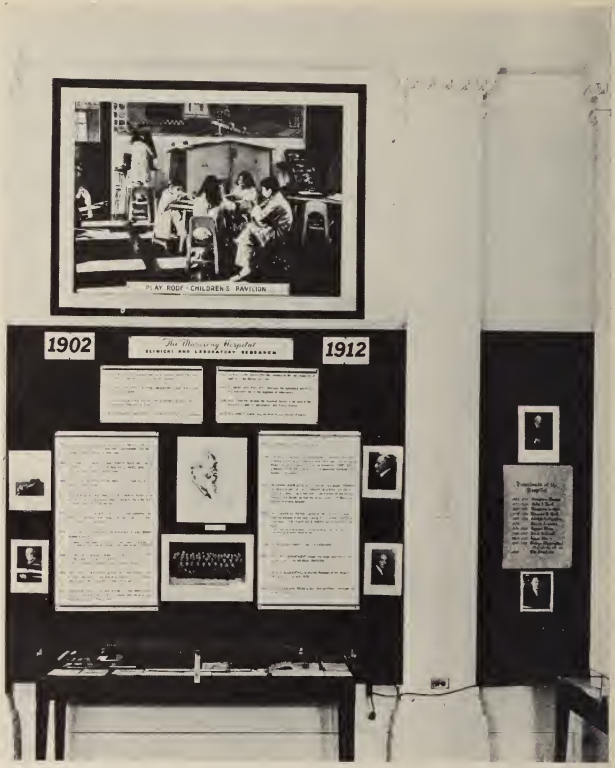


FIG. 6. Panel IV. For the printed matter on the two large placards see addendum

FIG. 7. Yankauer's ingenuity—Bronchoscope devised in an emergency out of gas pipe

"Blood Cultures in General Infections"; by Buerger's discovery of thromboangiitis obliterans; by Ottenberg, by A. A. Epstein, by Lilienthal's "First Thoracotomy under Intratracheal Anesthesia."

Panel V (1912–1932) (fig. 9) is devoted to "Service to the Nation," to the World War effort, and the participation of our hospital in that momentous strife. The hospital has moved to its new quarters. It has extended itself into many buildings, housing a population of a small town. A new generation of medical

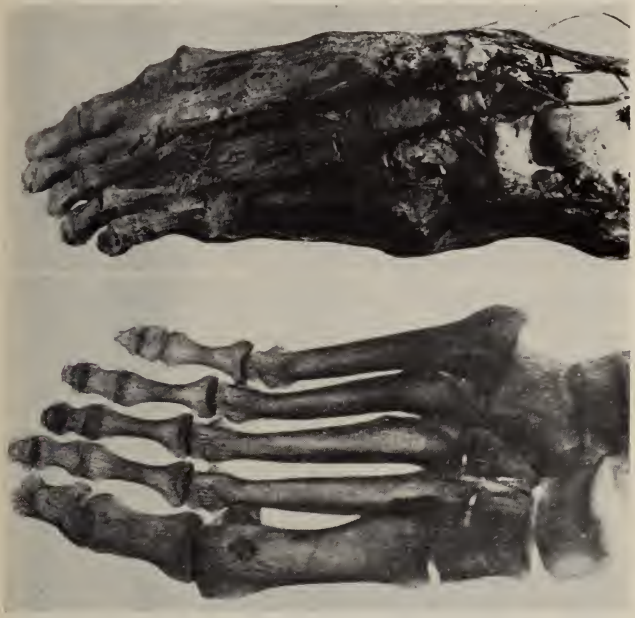


FIG. 8. Mummy's foot, and first x-rays taken at The Mount Sinai Hospital (1905)

men are producing outstanding work of scientific merit. The show case accompanying this panel is replete with reprints of the publications of this meritorious group and their accomplishments.

But shortly the war breaks and all effort and attention is strained at serving the nation. On this wall are shown a series of photographs of scenes and activities of Mount Sinai, Base Hospital #3 at Vauclaire, France. On this wall too, is exhibited the bronze placard recovered from the S. S. Lapland, the ship that carried the Unit to Europe. A bound volume of the activities and accom-

plishments of the Unit in France, abundantly illustrated, is also open to view.

The four large show-cases that occupy the center of the Exhibit Hall contain a miscellany of things interesting and of sentimental and historical value. In one case is seen a display of ophthalmoscopes illustrating the growth and

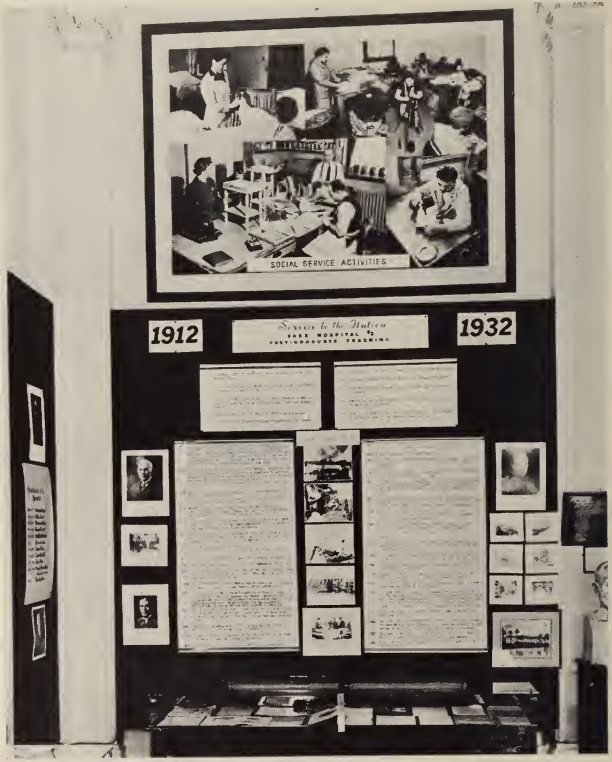


Fig. 9. Panel V. For the printed matter on the large placards see addendum

development of that instrument of precision; the collection features particularly the May prismatic ophthalmoscope devised by Dr. Charles H. May, while a member of the Hospital staff. The original diploma of Dr. Josephine Walter, dated 1885, is exhibited, granted to the first woman interne in America. Two

whole cases are devoted to the medals, the Certificates of Honor, and the Decorations for meritorious achievements. Included here are Foreign Orders, Legions of Honor, individual recognitions in the form of medals by institutions, certificates of merit in Scientific Exhibits to members of the staff. This whole display represents an inspiring recognition by the world at large of the efforts and successes of the hospital's scientific personnel (fig. 10).

In one corner of the Exhibit Hall a pilaster bears the list of honorary holders of the Welch and Janeway Lectureships. These names include many of the most celebrated living scientists of our day and time, a testimonial to the respect and thought which the world of scientific men hold for our institution. Not all living either, for the roll call of Welch Lecturers is headed by the late Dr. Richard Willstaetter, that most brilliant of biochemists, a fugitive from Nazi injustice, a guest of honor and distinction in our homeland.

On a final panel (fig. 11) we note the display of the present day activities of the Training School for Nurses, on which are depicted the daily routine of study, the education of the nurse-in-the-making, the teaching facilities, growth and development of that important arm of a growing hospital. Of particular interest is the model of the Mount Sinai Hospital bed, devised in this institution, now generally applied and universally recognized as a practical and ideal type of bed for the helpless sick.

The large room adjoining the main Exhibit Hall is devoted to present day scientific and clinical activities of the contemporary medical staff. A few, a very few, exhibits represent only a fraction of their recent achievements and activities. Space is much too limited to allow justice to be given to the innumerable scientific studies of the Staff in recent years. Just a flash, here and there, an outstanding accomplishment, an item of particular interest to the lay public, a simple but successful research that could, by demonstration, be made understandable to the visitors, is all that in a limited space can be accomplished.

But as the mosses grow on the old Manse, as the ivy interwinds its tendrils about the pachysandra in the Blumenthal garden, the Hospital assumes an air and atmosphere of maturity and ripeness. The world will, does follow a simple trail that leads to halls marked by ninety years of sincere effort and of no mean accomplishment. The lean and ardent years of this newer war will not mar the close of a century of continued urging, of scientific and social accomplishment, of betterment in the care and solicitude for the sick patient. As medicine progresses, The Mount Sinai Hospital will keep step; the years will lengthen—the sun and the shadows will undoubtedly play on the walls of a still greater and a still more acclaimed institution.

Burrill B. Crohn,
Chairman, Exhibit Committee

The Committee wishes to acknowledge and to thank Dr. Leon M. Arnold, Dr. Alvin Gordon, and Dr. Saul Jarcho for active and spirited cooperation in planning and arranging the Exhibit.

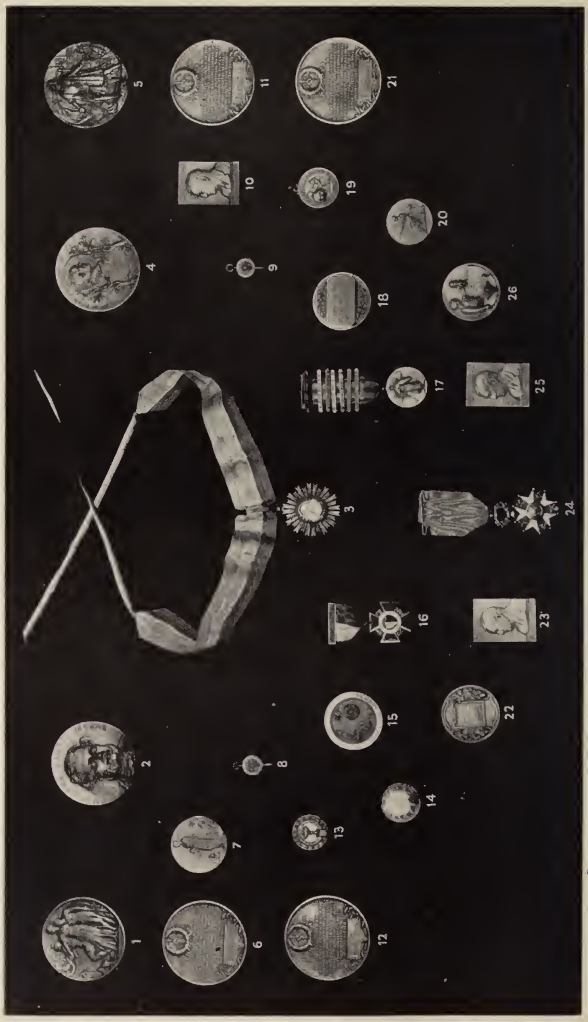


FIG. 10. Decorations awarded to members of the staff of the hospital for merit in science and research

1. Front view of medal presented to the late Dr. Edwin Beer, Dr. Howard Lilienthal, Mr. Charles Klingenstein and Mr. Benjamin Mordecai by the Trustees of The Mount Sinai Hospital for patriotic service during World War I. (See medals 6, 11, 12, 21.)

2. Townsend Harris Medal presented to Dr. A. A. Berg for notable achievement by the Associate Alumni of the College of the City of New York, 1941.

3. The decoration of the "Second Order of Bolivar" of the Republic of Venezuela, presented to Dr. A. A. Berg. This is the highest order that can be bestowed in the Republic. Only the President of Venezuela can receive the "First Order of Bolivar."

4. New York Academy of Medicine Medal presented to Dr. Bela Schick, 1938.

5. World's Columbian Exposition Medal awarded to The Mount Sinai Training School for Nurses, 1892.

6. Medal presented to the late Dr. Edwin Beer by the Trustees of The Mount Sinai Hospital for patriotic service during World War I.

7. The Addingham Gold Medal presented on April 12, 1938 to Dr. Bela Schick, "The person who has made the most valuable discovery for relieving pain and suffering in humanity."

8. Medal presented to the late Dr. Edwin Beer by the Societe Internationale D'Urologie, 1927.

9. Gold key awarded to Dr. William Bierman for distinguished contributions to the medical science of physical therapy by the American Congress of Physical Therapy.

Other recipients of this gold key award at the same time were. President Franklin D. Roosevelt; Dr. W. S. C. Copeman (at London, England); Mr. Bernard M. Baruch (Financier).

10. American Medical Association Gold Medal awarded to Dr. Moses Swick for original investigative work on intravenous and oral urography.

11. Medal presented to Dr. Howard Lilienthal by the Trustees of The Mount Sinai Hospital for patriotic service during World War I.

12. Medal presented to Mr. Charles Klingenstein by the Trustees of The Mount Sinai Hospital for patriotic service during World War I.

13. American Medical Association Gold Medal awarded to Dr. Bernard S. Oppenheimer for electrocardiographic exhibit illustrating pathologic physiology of the cardiac mechanism, 1917.

14. Gold Medal of the Canadian Medical and Ottawa Medical Associations awarded to Dr. Louis Gross for scientific exhibit, 1937.

15. First prize for scientific exhibit in physiology awarded to Dr. William Bierman by the American Congress of Physical Therapy, 1934.

16. Lucien Howe Medal awarded to Dr. Joseph H. Globus and Dr. Sidney Silverstone for meritorious work on brain tumor and visual field defects, 1935.

17. World War I Service Medal of Dr. Harold Neuhof. Each of the six bars represents participation in a major military campaign. The maximum number of bars possible is present.

18. First prize for scientific exhibit awarded to Dr. William Bierman by the American Congress of Physical Therapy, 1935.

19. Gold medal awarded Dr. Emanuel Libman for his exhibit on endocarditis, presented by the American Medical Association, 1912.

20. Medal presented to the late Dr. Edwin Beer for meritorious service by the American Congress of Physical Therapy, 1936.

21. Medal presented to Mr. Benjamin Mordecai by the Trustees of The Mount Sinai Hospital for patriotic service during World War I.

22. Medal awarded to Dr. William Bierman, Dr. Samuel Silbert and Dr. Mae Friedlander for a scientific exhibit by the American Congress of Physical Therapy, 1939.

23. American Medical Association Bronze Medal to Dr. Louis Gross for studies on the blood supply of the heart, 1937.

24. French Legion of Honor awarded to Dr. William Bierman, 1937.

25. American Medical Association Gold Medal awarded to Dr. Gregory Shwartzman for original investigations, 1934.

26. Medal awarded by the American Congress of Physical Therapy to Dr. William Bierman and Dr. Mae Friedlander for scientific exhibit, 1940.

ADDENDUM

The description placards of each historical panel are here reproduced. Each section marks a period and corresponding panel.

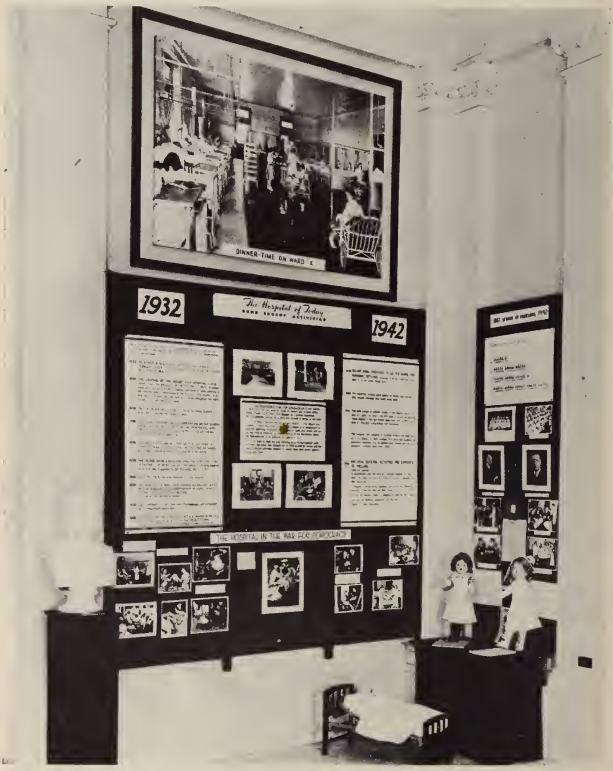


FIG. 11. Panel VI. For the printed matter on the two large placards see addendum

1852 to 1862

1852 THE JEWS' HOSPITAL in New York is chartered and founded. Sampson Simson is the first President (fig. 12). His co-founders are:

John M. Davies	Benjamine Nathan
John I. Hart	Isaac Phillips
Henry Hendricks	John D. Phillips
Rev. Samuel M. Isaacs	Theodore J. Seixas

1855 Doors of the Hospital are opened, on May 17, at 138 West 28th Street, between Seventh and Eighth Avenues. It is a four story building with

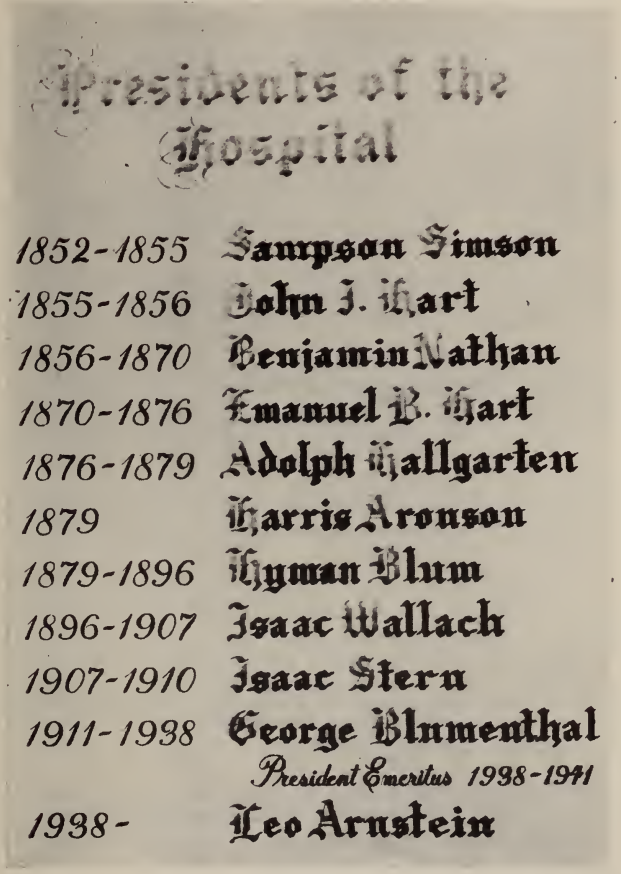


FIG. 12

45 beds. The staff includes VALENTINE MOTT, WILLARD PARKER, and other eminent physicians of the day. The first patient is Louis Seidner, operated on successfully for a fistula by Dr. Israel Moses.

1856 In its first full year, the Hospital admits 216 patients. Its operating expenses total $5,493.

1860 Dr. Abraham Jacobi, one of the foremost specialists in children's diseases, is appointed Attending Physician.

1862 The Hospital opens its wards to wounded Federal soldiers of the Civil War, installing additional beds and increasing its personnel for the purpose. In the same year, the Hospital treats many of the wounded in the New York Draft Riots.

1863 to 1882

1866 To make it clear that the Hospital serves the community without distinction of race or religion, its name is changed to The Mount Sinai Hospital.

1871 The Mount Sinai and Bellevue Hospitals treat those wounded in the Boyne Day riot between Irish and Ulster partisans.

1871 The Hospital has outgrown its original building. In this year it cares for 677 in-patients and 1,064 out-patients.

1872 The Hospital is moved into its new building,—a three and a half story structure of 120 beds on Lexington Avenue, from Sixty-sixth to Sixty-seventh Streets.

1872 The Medical Board and House Staff are organized, at a meeting at the home of Dr. Willard Parker, who becomes first Chairman of the Board.

1872 The Hospital takes a bold step forward by appointing two women, Dr. Ann A. Angell to the House Staff and Dr. Eliza Phelps as Apothecary.

1873 The Outdoor Dispensary (Out-Patient Department) is formally established. (The Hospital had treated out-patients from the beginning.) There are four divisions: Medical, Surgical, Gynecologic, and Children's. Dr. Paul Fortunatus Mundé becomes head of the Gynecologic Clinic. Dr. Mary Putman Jacobi, one of the most important pioneer women physicians, heads the Children's Clinic.

1877 The Medical and Surgical Services are separated for the first time. The House Staff is reorganized with junior physicians serving alternately in medicine and surgery. Dr. D. H. Davison is the first appointee under this plan.

1877 An in-patient Gynecologic Department is established, headed by Dr. Emil Noeggerath, pioneer in the study of gonorrhea.

1878 The first separate service in New York City for in-patient care of children is established at Mount Sinai, through a legacy from Michael Reese of California. Dr. Abraham Jacobi heads this department.

1879 Eye and Ear Services are organized, headed by Dr. Emil Gruening.

1880 Dr. Arpad G. Gerster, considered the first Listerian surgeon in America, is appointed Attending Surgeon.

1881 Stimulated by the Mount Sinai Ladies Auxiliary, the School of Nursing is established. Mrs. Florian Florance is first President, and Miss Kate Rich is first Superintendent.

1882 to 1902

1882 Mount Sinai is already outgrowing its second home, 1,692 in-patients are treated in the year, twice as many as ten years earlier.

1882 The Medical Staff includes Drs. Abraham Jacobi, Alfred L. Loomis, Henry N. Heinemann, and Julius Rudisch. The Surgical Staff includes Drs. Willard Parker, Thomas Markoe, Daniel L. Stimson, William F. Fluhrer, John Allan Wyeth, and Arpad G. Gerster.

1883 The Hospital building is enlarged to a capacity of 190 beds and an isolation building is added. Space for private patients is increased, indicating the emergence of the modern hospital as a medical center for all instead of an institution for the poor only.

1883 Dr. Edward Gamaliel Janeway, one of the greatest diagnosticians of his time, is appointed to the Staff.

1886 Mount Sinai grants its diploma to Dr. Josephine Walter, first woman in America to serve a formal internship.

1886 To relieve overcrowding of the Hospital and care for patients who can be treated at home, a District Medical Service is inaugurated, first of its kind in the city.

1887 Dr. William H. Wilmer is graduated from the House Staff. He later headed the Wilmer Ophthalmic Institute at Johns Hopkins University.

1888 Dr. Arpad G. Gerster publishes the first American work by an American author on Listerian surgery: "Rules of Aseptic and Antiseptic Surgery," illustrated with photographs taken in the operating rooms of The Mount Sinai and Lenox Hill Hospitals.

1888 Dr. Carl Koller, discoverer of local anesthesia, who introduced the use of cocaine for this purpose in 1884, is appointed to the Eye and Ear Department.

1888 Dr. Emil Gruening performs one of the pioneer Mastoidectomies in this country.

1890 The Dispensary (Out-Patient Department) is greatly expanded, housed in a new building. Neurological, Skin, and Venereal Disease Clinics are established.

1893 Notable additions are made to the Staff. Recognizing the growing importance of specialties, the Hospital appoints Dr. Bernard Sachs as Consulting Neurologist and Dr. Sigismund Gustgarten as Consulting Dermatologist. Other appointees include:

Dr. Henry Koplik, founder of the first sterilized mild station in the United States, later discoverer of Koplik's spots, important diagnostic sign of measles.

Dr. Howard Lilienthal, leader in development of chest surgery.

Dr. Nathan E. Brill, discoverer of Brill's disease, a form of typhus.

Dr. Morris E. Manges, subsequently professor of clinical medicine at Polyclinic and Bellevue Medical Schools.

Dr. Joseph Brettauer, a master technician in gynecologic operations.

Dr. Charles May, later to invent the May prismatic opthalmoscope (1916).

1893 The Laboratory is established, housed in a small room, with Dr. Henry H. Heineman as Pathologist and Dr. Frederick S. Mandlebaum as Assistant Pathologist.

1895 The Genito-Urinary Service is established, with Dr. William F. Fluhrer as its first chief.

1896 Dr. Bernard Sachs publishes his work on "Amaurotic Family Idiocy," later known as Tay-Sachs Disease.

1897 Appointed Assistant Pathologist, Dr. Emanuel Libman begins his work on Streptococcus enteritis.

1900 The Hospital purchases its first x-ray machine. Dr. Eugene Eising, House Surgeon, takes the first plate. A year later, Dr. Walter M. Brickner is appointed Radiographer.

1901 The cornerstone of the present group of Hospital buildings is laid, May 22, by Isaac Wallach, President.

1903 to 1912

1904 The new Hospital buildings are dedicated, on March 15, Dr. Sigismund S. Goldwater is appointed Superintendent. The ten buildings have a capacity of 456 beds.

1906 Dr. Emanuel Libman publishes "Experiences with Blood Cultures in the Study of Bacterial Infections," a pioneer study of bacteria in the blood stream.

1906 The Social Welfare Department is formed by Miss Jennie Greenthal.

1907 The George Blumenthal, Jr., Fellowship Fund is established, to aid and encourage research workers; this is the first allotment for work in the laboratory.

1908 Dr. Reuben Ottenberg, who in 1907 had performed the first blood transfusion with compatibility tests, points out that blood groups are hereditary.

1908 Dr. Leo Buerger describes Thromboangiitis Obliterans (Buerger's disease). A disease of the blood vessels of the extremities, usually resulting in gangrene. This study initiated work which eventually obviated, in most cases, the need for amputation.

1908 Dr. Emanuel Libman publishes "The Etiology of Subacute Infective Endocarditis." This work is fundamental in establishing the cause of infections of the heart valves.

1909 The Otologic Service is separated from Ophthalmology and Dr. Fred Whiting is made Attending Otologist. This is the first independent Otologic Service in a New York hospital.

1910 Dr. Nathan E. Brill publishes a study of a new infectious disease, which becomes known as Brill's disease, later recognized as the endemic form of typhus fever.

1910 The Dental Department is established.

1910 The Hospital begins formal post-graduate medical instruction, entering into its long, harmonious association with The College of Physicians and Surgeons of Columbia University. Drs. Brill, Libman, Gerster, and Berg are appointed Associate Professors at Columbia.

1910 Dr. Edwin Beer publishes his revolutionary paper "Removal of Neoplasms of the Urinary Bladder by Fulguration," describing a new and simple method of destroying tumors of the bladder by high frequency current. Dr. Beer is appointed Attending Surgeon.

1910 Dr. Howard Lilienthal performs the first thoracic operation for abscess of the lung, using intra-tracheal insufflation anesthesia. Dr. Charles Elsberg administers this anesthesia. Ether enters the throat by means of a catheter passed by mouth. The lungs are approached by an incision through the ribs.

1910 The Physiotherapy Clinic is established.

1911 The X-Ray Department moves into larger quarters on the ground floor of the Medical Pavilion.

1911 The Cystoscope Room is built and outfitted (enlarged and refitted in 1933).

1911 George Blumenthal is elected President of the Hospital, holding this office until 1938.

1913 to 1932

1913 A large building program is initiated. Funds are collected for the Children's Pavilion and Dispensary, Laboratory Building, Director's Home, Employees' Dormitory, and a new Adult Ward Building. About one-third of the funds are contributed by the children of Barbara and Meyer Guggenheim; the Laboratory Building is donated by Adolph Lewisohn.

1915 The Electrocardiography Department is established. The Hospital is presented with an electrocardiograph and the wards are wired for connection with the instrument. The instrument and wiring are among the very earliest in the United States. The electrocardiograph is a machine for recording the electrical impulses of the heart muscle.

1915 Dr. Richard Lewisohn introduces the Citrate Method of Blood Transfusion. This epoch-making improvement, by preventing the clotting of freshly drawn blood, makes a transfusion a simple, efficient operation.

1916 Mount Sinai organizes Base Hospital Number 3 of the United States Army Medical Corps. 24 physicians, 50 nurses and 153 inlisted personnel serve with this unit at Vauclaire, France.

1916 Mrs. Herbert H. Lehman leads in formation of the Social Service Auxiliary, women volunteers who attend to many wants of convalescing patients and of patients' families.

1916 Drs. Fred S. Mandlebaum and Hal Downey publish "The Histo-Pathology and Biology of Gaucher's Disease—Large Cell Splenomegaly."

1917 Dr. Albert A. Epstein—Nephrosis. A study of the chemistry of the blood and tissue fluids in forms of Bright's Disease.

1917 Dr. Sydney Yankauer is appointed Attending Laryngologist.

1919 The Children's Health Class is organized by Dr. Ira Wile.

1919 Dr. I. C. Rubin publishes his discovery of the use of "Peruterine Insufflation of the Fallopian Tubes" for the diagnosis and treatment of sterility in women.

1920 The Psychiatry Clinic (Mental Health Class), one of the earliest in a general hospital, is established by Dr. C. P. Oberndorf.

1922 The Hospital is expanded by the addition of three buildings: the Private Pavilion donated by Daniel, Murray, and Sol. R. Guggenheim; the Children's Pavilion, dedicated to Lewis and Milly Einstein by their father, Henry L. Einstein; the Blumenthal Auditorium, donated by Mr. and Mrs. George Blumenthal.

1922 Drs. A. A. Berg and Richard Lewisohn introduce and promote in America the operation of partial gastrectomy for removal of part of the stomach for ulcer, soon after the operation had been developed in Austria.

1923 Residencies are established in Ophthalmology, Pediatrics, Neurology, Gynecology, and Otolaryngology.

1923 Dr. Bela Schick, discoverer of the Schick test for susceptibility to diphtheria, is appointed Attending Pediatrician.

1924 The Occupational Therapy Department is established.

1924 Dr. Joseph H. Globus and Dr. Israel Strauss complete work on Spongioblastoma of the brain—first description of an important brain tumor.

1924 A Metabolism Clinic is established.

1924 Drs. Emanual Libman and Benjamin Sachs publish "A Hitherto Undescribed Form of Valvular and Mural Endocarditis."

1925 Dr. Howard Lilienthal publishes his "Thoracic Surgery," a classic, first of its kind in this country.

1925 Drs. Nathan E. Brill, George Baehr, and Nathan Rosenthal publish "Generalized Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen—A Hitherto Undescribed Type."

1926 Dr. Louis Gross, author of "The Gross and Microscopic Anatomy of the Blood Vessels in the Valves of the Human Heart," (1921) is appointed Director of Laboratories.

1926 The Clinical Pathological Conferences are established and are regularly attended by hundreds of physicians on Wednesday afternoons.

1926 Dr. Gregory Shwartzman is appointed Bacteriologist. Later he discovers the "Shwartzman Phenomenon." Local skin reactivity to bacterial filtrates.

1927 The new building of the School of Nursing is completed, accommodating 490 nurses. More than half of the cost is contributed by the Trustees of the Hospital.

1928 Drs. Robert T. Frank and Morris A. Goldberger publish their work on Female Sex Hormone in the blood.

1928 Dr. Joseph Turner succeeds Dr. Sigismund S. Goldwater as Director of the Hospital.

1930 Dr. Moses Swick publishes his work on Intravenous Urography (a method for x-ray diagnosis of kidney diseases).

1931 The Consultation Service is established for people of moderate means who are referred by their physicians.

1931 The new Semi-Private Pavilion is opened, a twelve-story building with 130 bed capacity, hailed as a pioneering development in hospitalization for people of moderate means. This raises the total capacity of the Hospital to 782 beds. A successful plan of Group Nursing, providing 24 hour nursing care at much reduced cost, is used in this Pavilion.

1931 Dr. George Baehr publishes "Renal Complications of Endocarditis."

1932 Regional Ileitis is described by Drs. Burrill B. Crohn, Gordon D. Oppenheimer, and Leon Ginzburg. An inflammatory disease of the small intestine, this widespread ailment proved amenable to cure by surgery.

1932 Drs. Harry Wessler and Harold Neuhof introduce their concepts of the pathology and treatment of putrid lung abscess.

1932 A separate Neurosurgical Service is created, with Dr. Ira Cohen at its head.

1933 to 1941

1933 To keep up the morale of convalescing patients, unemployed because of the depression, the Social Service Workroom is established.

1933 Dr. Asher Winkelstein describes a new treatment for Stomach Ulcer—Continuous Alkalinized Milk Drip into the Stomach.

1934 The Journal of the Mount Sinai Hospital is established under the editorship of Dr. Joseph H. Globus, to disseminate practical and scientific, medical and surgical data gathered at the bedside and in the laboratories of the Hopsital. The Journal is distributed to Universities and medical libraries throughout the world, as well as to private subscribers.

1934 The Hospital provides facilities and funds for exiled European scientists to resume their research work.

1935 Drs. George Baehr, Paul Klemperer, and Arthur Schifrin publish "A Diffuse Disease of the Peripheral Circulation Usually Associated with Lupus Erythematosus and Endocarditis."

1936 Arrangements are made with the Neustadter Home in Yonkers to receive Convalescent Patients from the Hospital—giving poor patients a chance to recuperate in the country.

1938 The Blood Bank is established under the direction of the Department of Hematology. The possibility of using preserved blood has been suggested by Dr. Richard Weil in 1915.

1938 Leo Arnstein becomes President of the Hospital.

1939 Drs. Harold T. Hyman, Louis Chargin, and William Leifer introduce "Massive Dose Chemotherapy of Early Syphilis by the Intravenous Drip Method." Syphilis—the five day intensive treatment.

1939 Radiotherapy is separated from Roentgenology and established as an independent department.

1939 An Electroencephalographic Unit is established at the Hospital for use in the diagnosis of Intracranial Lesions. An electrical recording device which simplifies diagnosis of diseases within the brain.

1940 Mount Sinai prepares to do its share for national defense—organizes General Hospital Number 3 of the United States Army.

1940 The Hospital collects blood plasma for Britain—approximately 260 people volunteer their blood every week.

1941 The total number of patients treated in the Hospital during the year is 17,222, to whom 236,492 days of service are rendered. Those treated in the Out-Patient Department total 27,654, with a total of 339,965 consultations and treatments.

The Hospital now occupies 18 buildings, covering the larger part of three city blocks; its staff numbers 900 physicians, surgeons, and laboratory scientists, and is administrative, nursing and service personnel numbers more than 1,400.

1941 National Defense Activities are expanded to include:

First-Aid courses

A catastrophe unit for service wherever needed in New York City and for care of disaster victims brought to the Hospital.

Emergency ambulances operated by American Women's Voluntary Services and the Red Cross

Training of Nurses' Aides in cooperation with the Red Cross.

Lectures on medical problems in the war

Course on War Neuroses

CONFERENCE ON VENEREAL DISEASE CONTROL NEEDS IN WARTIME

Under the Auspices of the U. S. Public Health Service

SURGEON GENERAL THOMAS PARRAN, *Presiding*

In conjunction with The Eighth Annual Meeting of the American Neisserian Medical Society

Hot Springs National Park, Arkansas

October 21 to 24, 1942

Venereal disease and America's war effort will be discussed by high-ranking medical officers of the War and the Navy Departments, prominent physicians, health officers and others at a Conference in Hot Springs National Park, Arkansas, October 21–24, 1942. Headquarters will be at the Arlington Hotel.

The Conference will be held under the auspices of the United States Public Health Service in conjunction with the Eighth Annual Meeting of the American Neisserian Medical Society. Surgeon General Thomas Parran will preside. State and local health officers, venereal disease control officers, practicing physicians, and all others engaged in venereal disease control activities are urged to attend.

Subjects for discussion will include venereal disease control measures influencing the war effort, epidemiology of syphilis and gonorrhea—1942, wartime venereal disease control education, research influencing the wartime venereal disease control program, and technics of venereal disease education.

Governmental, professional and health organizations to be represented at the Conference include: the War Department, the Navy Department, the Social Protection Section of the Office of Defense Health and Welfare Services, the American Medical Association, the American Neisserian Medical Society, the American Social Hygiene Association, State and local health departments, and the United States Public Health Service. The following is a tentative program of the Conference.

October 22, 10 a.m.—Session I

VENEREAL DISEASE CONTROL MEASURES INFLUENCING THE WAR EFFORT

Welcome Address—*Surgeon General Thomas Parran*

1. Rehabilitation of Selectees with Syphilis and Gonorrhea—*Lt. Col. Richard H. Eanes,* Asst. Dir., Medical Division, Selective Service System
2. Present Venereal Disease and Prostitution Problems as They Relate to the Army—*Lt. Col. T. B. Turner,* Director, Venereal Disease Control Division, Preventive Medicine Service, United States Army
3. Present Venereal Disease and Prostitution Problems as They Relate to the Navy—*Captain C. S. Stephenson,* In Charge, Division of Preventive Medicine, Bureau of Medicine and Surgery, United States Navy

4. The Contribution to the War Effort of the Subcommittee on Venereal Diseases, National Research Council—*Dr. J. E. Moore,* Baltimore, Md.
5. Private Physician Support of the Wartime Venereal Disease Control Program

October 22, 2 p.m.—Session II

THE EPIDEMIOLOGY OF SYPHILIS AND GONORRHEA—1942

1. The Epidemiology of Gonorrhea as a Stimulus to Prostitution Repression—*Dr. Donald H. Williams,* Medical Director, Division of Venereal Disease Control, Provincial Board of Health, Vancouver, B. C.
2. Improvement of Present Methods for Extrafamilial Contact Tracing—*Miss Mary A. Burke,* Consultant in Social Hygiene Nursing, Detroit Department of Health
3. Difficulties in Case Holding of Selectees Infected with Syphilis—*Dr. G. Foard McGinnes,* Director, Division of Venereal Disease Control, Tennessee State Department of Health
4. Defects in the Present Follow-up Program—*Lida J. Usilton,* Principal Statistician, Division of Venereal Diseases, U. S. Public Health Service
5. The Male Investigator in Venereal Disease Control Follow-up—*Dr. Malcolm H. Merrill,* Chief, Bureau of Venereal Diseases, California Department of Public Health

October 23, 9:30 a.m.—Session III

EIGHTH ANNUAL MEETING, AMERICAN NEISSERIAN MEDICAL SOCIETY

1. The Control of Venereal Disease Among Industrial Workers—*Surgeon Otis L. Anderson,* Assistant Chief, Division of Venereal Diseases, U. S. Public Health Service
2. Organization and Management of Clinics in a State Gonorrhea Control Program—*Dr. F. W. Caudill* and *Dr. R. E. Teague,* Kentucky State Department of Health
3. Gonococcal Culture Methods—*Dr. Charles M. Carpenter,* School of Medicine, University of Rochester
4. Management of Gonorrhea in the Male—*Dr. P. S. Pelouze,* University of Pennsylvania, Philadelphia
5. Management of Gonorrhea in the Female—*Dr. Robert M. Lewis,* Yale University School of Medicine
6. Hyperpyrexia in Chemoresistant Gonorrhea—*Dr. Stafford L. Warren,* School of Medicine, University of Rochester

General discussion of the above panel led by *Dr. Nels A. Nelson,* Director, Division of Venereal Disease Control, Maryland Dept. of Health, and *Dr. Adolph Jacoby,* New York City Health Department

October 23, 2:00 p.m.—Session IV

EIGHTH ANNUAL MEETING, AMERICAN NEISSERIAN MEDICAL SOCIETY

1. Gonococcus Cultures as a Public Health Service—A Preliminary Report—*Captain Daniel Bergsma,* Venereal Disease Control Officer, Headquarters, First Army, Governors Island, N. Y.

2. President's Address—*Assistant Surgeon General R. A. Vonderlehr*, Division of Venereal Diseases, U. S. Public Health Service
3. Gonorrhea from the Standpoint of the Army—*Captain Ernest B. Howard*, Venereal Disease Control Officer, Fourth Army Corps Area, Atlanta, Ga.
4. Gonorrhea from the Standpoint of the Navy—*Captain C. S. Stephenson*, In Charge, Division of Preventive Medicine, Bureau of Medicine and Surgery, United States Navy
5. Résumé of the Year's Research in Gonorrhea—*Dr. Alfred Cohn*, Department of Health, New York City
6. The Rôle of Organized Medicine in the Control of Gonorrhea—*Dr. Robert S. Breakey*, Lansing, Michigan

October 23, 2:00 p.m.—Demonstration

TECHNICS OF MODERN SERODIAGNOSTIC TESTS FOR SYPHILIS

October 24, 9:30 a.m.—Session V

WARTIME VENEREAL DISEASE CONTROL EDUCATION PROGRAM

1. The Relationship between the Programs of Venereal Disease Control Education and the Repression of Prostitution
   a. From the point of view of public health—*Dr. George M. Leiby*, Director, Division of Preventive Medicine, Louisiana State Department of Health
   b. From the point of view of social protection—*Mr. Charles P. Taft*, Assistant Director, Office of Defense Health and Welfare Services
   c. From the point of view of the public—*Mr. Capus Waynick*, Director, Demonstration of Public Health Education Measures in the Control of Venereal Diseases, Raleigh, N. C.
2. The Venereal Disease Control Education Program in the Armed Forces
   a. Army—*Major William A. Brumfield*, Venereal Disease Control Division, Preventive Medicine Service, U. S. Army
   b. Navy—*Captain C. S. Stephenson*, In Charge, Division of Preventive Medicine, Bureau of Medicine and Surgery, U. S. Navy
3. The Current Status of Venereal Disease Education—*Surgeon General Thomas Parran*, U. S. Public Health Service

October 24, 2 p.m.—Session VI

RESEARCH INFLUENCING THE WARTIME VENEREAL DISEASE CONTROL PROGRAM

1. Progress in Investigations of the Intensive Therapy of Syphilis—*P. A. Surgeon Harry Eagle*, U. S. Public Health Service Syphilis Research Center, Baltimore, Md.
2. New Serologic Tests for Syphilis and Their Demonstrated Efficiency—*Dr. Arthur H. Sanford*, Mayo Clinic, Rochester, Minn.
3. Progress in the Wartime Management of Gonorrhea—*Dr. P. S. Pelouze*, University of Pennsylvania, Philadelphia

4. Relationship between Venereal Disease Control and the Joint Army and Navy Committee on Welfare and Recreation—*Brigadier General F. H. Osborn,* Chief of Special Service, United States Army
5. Problems Involved in the Adaptation of Recent Scientific Discoveries to the Wartime Control of the Venereal Diseases—*Dr. John H. Stokes,* University of Pennsylvania, Philadelphia

October 21, 2 p.m.

TECHNICS OF VENEREAL DISEASE EDUCATION

1. Introductory comments—*Assistant Surgeon General R. A. Vonderlehr,* Division of Venereal Diseases, U. S. Public Health Service
2. Presentation of a Typical Venereal Disease Education Problem for Discussion by Panel and Conference

Chairman:

Participants: the entire conference membership

Discussion Leaders:

State Health Officer:
Dr. Felix J. Underwood
Executive Officer
State Board of Health
Jackson, Mississippi

State Venereal Disease Control Officer:
Dr. Malcolm H. Merrill
Chief, Bureau of Venereal Diseases
Department of Health
San Francisco, Calif.

Local Health Officer:
Dr. Hugh Leavell
City Health Officer
Louisville, Ky.

Local Venereal Disease Control Officer:
Dr. L. W. Shaffer
Director, Social Hygiene Division
Department of Health
Detroit, Michigan

Community resources:
Dr. Lucy Morgan
Health Education Consultant, P.H.S.
Community Organization for Health Education
Fayetteville, N. C.

Voluntary Health Agency:
Dr. William F. Snow
General Director
American Social Hygiene Assn.

Press:

Radio:

Health Dept. Public Relations:
Miss Ann Wilson Haynes
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Department of Public Health
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Clinic Management:
Dr. Nels A. Nelson
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State Department of Health
Baltimore, Maryland

Gonorrhea:
Dr. Charles M. Carpenter

School of Medicine
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Syphilis Case-control:
Miss Anne Sweeney
Vanderbilt University Hospital
Nashville, Tenn.

Gonorrhea Case-control:
Mr. Morris S. Wortman
University of Missouri
Columbia, Missouri

Social Protection:
Mr. Arthur E. Fink
Regional Supervisor
Division of Social Protection
Birmingham, Alabama

Work Projects Administration:
Mr. T. Lefoy Richman
Informational Specialist
U. S. Public Health Service

Nursing:
Miss Donna Pearce
Public Health Nursing Consultant
U. S. Public Health Service

General Health Education:
Miss Elizabeth Bohnenberger
Director of Health Education
State Board of Health
Jacksonville, Florida

VENEREAL DISEASE EDUCATIONAL DISPLAY

Demonstrations of use of publications, posters, motion pictures, radio, etc.

Manuscripts, abstracts of articles, and correspondence relating to the editorial management should be sent to Dr. Joseph H. Globus, Editor of the Journal of The Mount Sinai Hospital, 1 East 100th Street, New York City.

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TO

DR. BARNEY (BERNARD) SACHS

THIS VOLUME IS DEDICATED

ON THE OCCASION OF THE SIXTIETH ANNIVERSARY

OF HIS ACTIVE PARTICIPATION IN THE

PRACTICE AND SCIENCE OF MEDICINE

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WISHES TO EXPRESS ITS APPRECIATION

TO THE MOUNT SINAI HOSPITAL

FOR MAKING POSSIBLE THE DEDICATION OF THIS

SPECIAL ISSUE OF THE JOURNAL

TO OUR BELOVED AND ESTEEMED COLLEAGUE,

DR. BARNEY (BERNARD) SACHS,

WHO FOR ALMOST HALF A CENTURY

HAS GIVEN DEVOTED SERVICE

TO THE MOUNT SINAI HOSPITAL,

THE NEUROLOGICAL SERVICE OF WHICH HE INAUGURATED

Bernard Sachs

FOREWORD

When a man past the biblical span of normal life duration becomes elected President of an international congress made up of the most eminent workers in his profession throughout the world, one must ask oneself by what means and for what reason has this thing come about.

The age, at that time, was not sufficient, seventy-three years, to endow its owner with dignity, authority and priority in its own right. There must have been other integers in this equation. There must have been a race well run—a happy fight well fought. Was it enormous intellectual achievement? Partly; for our friend has as much originality as becomes a man; through it, his patronymic has become graven on the *tabula rasa* of the mind of every undergraduate in medicine throughout the civilized world.

But there must have been more than even the exactly right quantity of originality. There must have been *zest:* a precious vital strength, making its owner interested and communal with all about him. The zestful man unites with the forces around him, adds his strength to theirs, or, with all his power, puts himself mightily in opposition. However, whether he be for or against, he has happiness in the enterprise and goes forth in comradeship to battle, and if there be enough zest, he finds no end of causes to fight for, and he will also in like fashion pick up the gauntlet on the ready.

But then again, not even the requisite originality and zest are quite enough to reach eminence among one's colleagues without political acuteness or self-seeking rumination. But an elevation reached circuitously little pleases him who has reached it, and Bernard Sachs has had a conscious joy in all that he has done. Therefore, he must have reached that place, not only by reason of his original mind, and by the drive of his zest, but also by the obvious integrity of his purpose; for here is a man whom one could know as honest and of good repute if one stood with him beneath a bridge for ten minutes in shelter from a shower of rain. He can think ill of no one, nor can he stoop to look for poorish qualities in any. Some befrilled unfunny ideologies he has fought with a passion born of his zest, like a combination of Roundhead and Maccabee, because he truly feels that "goodness" and "badness" do not live in a solution of relativity in the middle of the alphabet, but are, and always will be *alpha* and *omega,* the beginning and the end. He has lived long enough to see the twilight of his enemy and the resurrection of the older virtues. He has seen fruit come from his labors and this volume is an earnest of the love he has earned from those he has taught, from those he has helped and from all who knowing him must needs bear great affection for him.

Foster Kennedy

HISTORICAL FRAGMENTS ON THE NEUROLOGICAL AND PSYCHIATRIC SPECIALTIES

Factors and Results in an Eminent Medical and Specifically Neurological Career

ADOLF MEYER, M.D.

[*Baltimore, Maryland*]

It was a most welcome and highly appreciated opportunity to be invited to join the many friends and colleagues determined to honor a man who, for so many years stood, and to this day stands, as the eminent neurologist and a highly esteemed leader in the medical profession of our greatest metropolitan center. It so happened that at the very time of the invitation I was preoccupied with the problem of the relation of neurology and psychiatry as part of a broader historical and factual as well as theoretical study of the factors figuring in determining the choice between a career preeminently in neurology or in psychiatry, and incidentally throwing more light on contemporary developments in the pertinent fields. There are certain components in the distinguished, and in many special ways, illuminating career of our colleague and friend, not only giving concreteness to an enviable personal record, but at the same time arousing many associations with events having an outstanding share in the shaping of a remarkable epoch in the development of medicine and of cultural perspectives.

To one with a similar start, but led preeminently into psychiatry, it becomes a fascinating temptation to look into the special course of events that led another to his career preeminently in neurology, and we shall see how there proved to be similarities and parallels in the development of Bernard Sachs and myself that gave origin to a special meaning for this historical fragment, fitting into my own preoccupations of these days, and also the desire to join those who pay tribute to the neurologist. A glimpse into the bibliography of Bernard Sachs contained in the Semi-Centennial Volume of the American Neurological Association, edited by Frederick Tilney and Smith Ely Jelliffe, made me aware for the first time of interesting parallels in our careers.

There is a real fascination about the particular skills and performances shaping themselves into medical specialties, and none comes closer to the very essence of the specifically *human* nature than the preoccupation with that strangely silent, but wonderfully built organ, the nervous system and brain and the development of the personality. This organ expresses itself equally significantly through its inherent and recondite structural differentiation, and, through its determining share in making of man both a neurologically integrated organism, and, through the special cerebral equipment the person as a unit, the carrier of our culutre and of social as well as individual life—the condition for the continuity and cohesion of life-times.

It is here the cultural evolution of man steps in.

Throughout, the nervous system had gradually come to play a late but telling role in scientific inquiry; but no period had been more rich and promising in new developments than that of the second half of the nineteenth century and the beginning of the twentieth, since a few cases of lesion with loss of man's distinctive feature, speech, and, after the discovery of electrical phenomena by du Bois-Reymond, the distinction of specially responsive areas by Fritsch and Hitzig gave the signal for "localization" of cerebral functions, involving increasingly tangible correlations and more than mere sidelights on bringing mentality into the center of objective as well as subjective concern. The physician, working with "man in trouble," became eager to seek the places of happenings and of functional dependence in the so far most non-demonstrative organ and in the most wonderful but perplexing behavior and mentation, and the wealth and unity of organismal and social integration. Only quite lately has the brain come to betray its kind of active life in potentials, which write for us their, to be sure far from plain, "transcription" of at least something going on in a responsible organ that had come close to being looked upon as little more than a mechanical exchange. The brain today is recognized as the most intriguing and fate-determining part—or shall we say tool or organ—of nature, and at last open to understanding and control through what we know most clearly only in the action of the whole entity, the person. Those who had to begin physician-fashion with the study of the corpse, today look to the nervous system for some kind of lock and key performance between what, after all, we know best in live man and his biographic record and setting, rather than in the dead body we had to study, and the mere animal experiment, and what we get from electrical stimulation. Today, more and more prepared to see and record life in *action*, we link both work and worker in man's nature and culture, and sense the order and regularities in health and disease of the nervous system in the setting of the ever-moving and ever-acting entity.

In keeping with this scientific and practical development, man's spirits, for centuries largely the domain of great abstraction, have been brought down to earth from the philosophical and theological heavens, and the eschatological soul drawn up from the depth of the earth's interior and the inferno—to be persons, beginning to seem real to the understanding in intensive and concrete studies of actual life, not only events and performances, but with more and more interest in the evolution and working, of the brain and of the individual as the infant and child and adolescent and adult and senescent, and its fate in health and disease—despite the courthouse of Dayton, a problem of nature and the big world of actuality, with heaven and hell in the flesh and the spirit of the individual, true and sharing his life with the group.

What had culminated with Descartes in a study of mind *and* body and their tenuous "interdependence," now entered upon a pursuit of the more and more active concept of Spinozist unity, and the demand for a culturally as well as scientifically intelligible and fruitful conceptual understanding and enlightenment of life, rather than the agelong pondering over the fate in an eternity entered through death, and a merely morphological display of brain structure;

so that what is accessible and open to progressive creative cultivation could replace what, as dependent on revelation and tradition, had found us entangled in deplorable and destructive aberrations of *de*volution and a dreary pessimism of fall from perfection and hope of redemption, instead of a creative urge and ambitions and pursuit of *e*volution. Without iconoclasm and surrender of ideals, indeed with a sense of vital reality and inductive idealism, a science of man as a reactive and creative entity with interest in progress, not merely in destruction, came to be our practical and ideal concern, and an inspiration to a constructive outlook of its science.

Sciences organize themselves around problems and outlooks or special topics and materials, and also around special human individuals and groups devoted to special studies and masteries and methods and opportunities. Objective significance and personal understandings intertwine, and it is humanly and factually important that we should want to trace these interlacings as actuality and in the light of the history and of new goals. Nobody could be more constantly confronted with both the differentiation and the reciprocity of the factors and the agents and those affected and involved, than the ones who have to work with man in need of help in what makes of man the whole or integrate. What leads man to espouse those medical specialties which the person, and the individual and group, and also with the organ of organismal and person integration, the nervous system, and finally with the outstanding person-functions as human soul and mind? There are those who focus more on the product, or on the functioning, and others are more concerned with the organs and their structures and mechanics. How do they come to specialize? Then there are those who see the task and opportunity and goal only in the sick, and others who learn to sense it in all of us, the well and the sick, the young and the old, the good and the bad.

Bernard Sachs is one of those who was led, or headed early in the direction of man as individual and integrator as person, and he focussed mainly on the neural integrator, as neurologist. As one similarly started but particularly bent on working with the whole product, with man as agent, the person and group, the present writer is interested in what makes for this difference of interest and perspective. For person-function, in the English-speaking countries, only our generation has felt the need of a special and distinctive term, "psychiatrist," or ergasiatrician. The specialty had existed as that of nervous and mental disease, and there had been "alienists," deciding and testifying on "alienation" and commitments, and those taking care of the "committed." But what has happened that has led to the creation of the *psychiatrist*, the physician specialized in the study and treatment of mental disorders as we see him today? Will the attention to some of the pertinent developments throw any light on the nature of what is to be distinguished as the concern mainly of the neurologist or mainly of the psychiatrist?

According to *Who's Who in America*, Dr. Bernard Sachs started his active career as "physician," in an early edition already "well-known as specialist in nervous diseases," and later as "neurologist, formerly alienist and neurologist

at Bellevue." In 1890 he was Professor of Mental and Neurological Diseases, but in the later editions of *Who's Who*, and at The Mount Sinai Hospital, he limited himself to "neurology." Considering the specific issue of this paper, those facts, and especially the writings and contemporaneous developments which are related to psychiatry, will be our main concern.

Bernard, known to his friends as Barney, Sachs was born in 1853 in Baltimore, but was brought up in New York, where his father had become a leading educator. He had his college training at Harvard from 1874 to 1878. According to his own reminiscences, to some extent under the influence of William James, he became interested in philosophy and psychology, and developed the intention to devote himself to medicine and particularly to the diseases of the mind. His brother Julius, nine years older, who had already launched upon his well known career as educator, following his father's footsteps, had returned from studies abroad, and Bernard planned to take his entire medical course there.

His choice fell on the new medical center of Strassburg (1878–1882) which Germany had manned with the flower of its young investigators after the conquest of Alsace. It was an unusual group—with the anatomist Waldeyer, who had stimulated his Hungarian pupil Mihalkovics to work out his embryology of the human brain as early as 1877, and who himself later, in 1890, gave the neurone theory its wider introduction to the medical world; with Goltz, and his unrelenting scrutiny of all hasty cerebral localizations; with Kussmaul, who as internist contributed to the study of speech disorders, but also had, as early as 1859, written his study of the infant; with von Recklinghausen, the pathologist who gave his name to a condition of fibromatosis apt to make serious impressions on the nervous system; and Hoppe-Seiler and Schmiedeberg, the founders of a most important school of pharmacology and of medical chemistry. It was an illustrious and inspired group. Krafft-Ebing had started to lay a foundation for the Cinderella, psychiatry, in 1872, but had soon left disappointed. He was replaced in 1873 by a friend of von Recklinghausen from their Würzburg days, Jolly—who succeeded only in 1886 in opening his long and carefully planned special clinic, four years after Bernard Sachs had finished his studies in Strassburg. Sachs has an early contribution in neuro-physiology to his name, pubpublished in *Pflüger's Archiv* of 1881, "On the Influence of the Spinal Cord on the Secretion of Urine." But there is no evidence of early attention on his part to psychiatry in Strassburg. Postgraduate work in Berlin, Vienna and London (1882–84) became more and more focussed on Sachs's final goal, that of joining the noteworthy group of neurologists and psychiatrists of his native land.[1]

While abroad and with his return to New York, Sachs had plenty of occasion to carry a challenging sense of the habitual neglect of American achievement

[1] Here I lack the account of specialist and cultural influences Sachs enjoyed and partook in, and that may have revived the Jamesian influence. I also lack any statement of just how it was that mental disease came to be an item of concern in his college days and philosophy. I might gain a lot from a few concrete data on centers of attention, travel and contacts at Strassburg and elsewhere.

by the European colleagues. He had a full realization of the vigorous group of workers and work asserting itself in his home territory, full of energy, but evidently also more on neurological than on psychiatric ground. The seventies and eighties were altogether a time of rapidly growing knowledge of neuro-anatomy and neuro-physiology, and creation and almost idolatry of clinical types, and election to the Olympus based on the die-hard cult of diagnosis and treatment of diseases, rather than human beings in distress. Neurology met with widespread appreciation and encouragement in its own right under Fritsch and Hitzig and Erb and von Leyden, and Charcot and Vulpian in Paris, and in London the Queen's Square group, and as a help to the budding of neuro-surgery, with Horsley as the first leader, and Sachs' friend, Arpad G. C. Gerster, and later Cushing in this country. With localization as a favorite preoccupation also among many internists, neurology was bound to promise a fascinating career as a specialty among a stimulating and responsive group of workers in the new era of medical work. Psychiatry was more strikingly local—German and French and Italian and British and Russian. In America, as we shall see, psychiatry was represented by State and private hospitals, by a fair amount of practice and non-institutional work, by medico-legal consultants, and by some lectures and some noteworthy books, of which the *Treatment of Insanity* by John M. Galt, 1846, and *Mental Hygiene* by Isaac Ray, 1864, were two of the earliest.

That Sachs, with all this background, developed so largely in the neurological direction is of real interest. He did not forget his first premedical leaning to the study of mental disease, but attained his actual satisfaction from the neurological angle. With his family known as educators in New York, where the field of neurology was developed to a high point, with psychiatry at best a collateral concern of livelihood and lecturing, Sachs could not help becoming an active member mainly of the neurological group. Sachs became most closely associated with Edward Constant Seguin, probably the most prominent and effective of the neurologists, but then at the point of gradual retirement. In Seguin Sachs recognized a great master of clinical exposition, and keenness of therapeutic interest. In the wider American Neurological Association he also found a warm reception and role through becoming the co-editor, and in 1886 to 1890, sole editor of the *Journal of Nervous and Mental Disease*. Only a few men were closely attached to psychiatry, but those who made psychiatry actually their life career were a group apart, attached to their institutions.

It will be important for the understanding of the attitude at the time to outline briefly the status of what non-institutional psychiatry there was. Foremost in actual productivity was Spitzka, who, with his three years of training in embryology and anatomy and psychiatry in Leipzig and Vienna from 1873–76, had pursued the morphological interests implanted by Schenck and Meynert, while in practice he became "surgeon and consulting neurologist." As early as 1874 Spitzka had become the winner of two rewards—one of the British Medico-Psychological Association for an essay on *Somatic Etiology of Insanity* and one on *Physiological Effects of Strychnia* obtained from William A. Hammond and the American Neurological Association. In 1883 he had published his remark-

ably good presentation of *Insanity*, far from being a mere rendering either of traditional asylum practice, or merely the teachings of the Vienna and other European schools. Psychiatric practice at the time no doubt received more attention through medico-legal glamor, as seen in Spitzka's own reputation largely through the trial of Guiteau, the assassin of President Garfield in 1881 (in which Spitzka was the only expert standing for the man's insanity). Two of Spitzka's pupils, Clevenger and Kiernan of Chicago, are among the few who came to contribute to psychiatry, and whom I came to know in 1892. Allan McLane Hamilton was the prototype of the medico-legal "alienist." William Alexander Hammond, a psychiatrist and neurologist risen from the rank of army physician to that of Surgeon-General, had published in 1883 his treatise on *Insanity in its Legal Relations*, but was no longer in New York when Sachs returned. The impetus of psychiatric opportunities closer to general hospitals that developed through the influence of Griesinger in the central European specially equipped city and university clinics, and the resulting substantial psychiatric work, especially in the German and Austrian and French and Italian centers, and Scotland and England, could not for a long time be developed in the American civic and political mal-organization, cultivating at best its none too satisfactory admission ward at Bellevue, and a few closed private institutions, "Bloomingdale," the Hartford Retreat, the McLean, the Butler Hospital, and the Kirkbride in Philadelphia, leaving to the State the more fully organized centers of acute and protracted care under commitment.

There was no doubt of the preponderance of actual neurological interest in the ranks of American medicine. The representatives of psychiatry had their association long limited to the "Medical Superintendents of American Institutions for the Insane," but in 1893 they opened their ranks to the non-institutional and adopted the British term as "American Medico-Psychological Association." The American Neurological Association, started 1875, had a few psychiatrically recognized members, but after all consisted definitely of neurologists, with S. Weir Mitchell and J. E. Jewell and William A. Hammond and J. J. Putnam and C. K. Mills in the lead, and with Spitzka largely as the one active experimental neuro-anatomist rather than for his status as psychiatrist.

There was also another development in the field of neurology and psychiatry. There had arisen a new element in the ranks of American medicine, one that was more akin to general and neurological practice than to official psychiatry, for the training and practice of which one was largely tied to residence in the institution. J. Ramsay Hunt, in Tilney and Jelliffe's *Semi-Centennial Anniversary Volume* of the American Neurological Association, covering the period from 1875 to 1924, gives a vivid description of the accession of George M. Beard of "neurasthenia" fame. He came to the second meeting of the illustrious body, June 1876, with his first contribution on the "Influence of Mind in the Causation and Cure of Disease and the Potency of Definite Expectation." The full account of the paper and its reception is one of the most illuminating records of the difficulty medicine had in rising above fixed tenets. "Expectations," Beard's word for suggestion, and the role of fear, and the emphasis on "nervous exhaus-

tion" in nervous disease brought mind, or what I now should call "man as person," into medical consideration—largely as part of "neurology," since nobody could have wanted it to be included in psychiatry, so definitely the job of the asylum. Beard considered fear, terror, anxiety and care, grief, anger, wonder and expectation as emotions, when active and unrestrained, potentially most effectual in producing disease and aggravations,—and with reason, hope, joy, resolution, ambition, self-confidence and expectation equally important as elements contributing to recovery. This insight had no doubt been recognized and used and tremendously abused, but had here come to be used, as he put it, in well-considered experiment. Effects could be brought about as permanent as those realized through the agency of medicines or electricity, applied to acute and chronic, functional and organic disease. What he called mental therapeutics, influence of the mind over the body whether in health or disease, should receive positive attention and a more thorough study of the subject for the purpose of availing oneself of its highest advantages, not for deception but with purpose, and with definite experiments. Dr. Hammond identified that, all or none fashion, with joining the theologians; Dr. Putnam did not believe it proper to state to one's patients what one did not know positively; he regarded the experiments as unscientific because the emotion could not be isolated. Even the matter of warts and their cure was brought up, obviously matters and questions to be systematically tried and inquired into. The fear and resistance to such unorthodoxy is one of the points no doubt playing a role in the attitude toward mental facts and mental disease.

Beard discussed Mental Therapeutics at the American Neurological Meeting of 1877, transmission of electric influence across the middle line of the body in 1878; morbid fears; symptoms and diagnosis of insanity, but also his share in "dosage of electricity" and Franklinism (1881), no doubt as much a vehicle for suggestion as the regulation neurologist's resources.

But by the time Sachs joined the American Neurological group, S. Weir Mitchell had reabsorbed Beard's field under the heading of rest-cure, based on "fat and blood," but with his keen practical sense probably more important than any neurologizing or broadly medical theories. In the main, any tendency of respect and attention for the mental dynamics was side-tracked into lay hands and religious movements. Since 1869 Seguin had given some lectures on mental disease in his neurological course. But the type of facts G. M. Beard discussed had passed, with his death in 1883, largely into the domain of what was classed as negligible common sense, and thus had no particular chance to counteract or modify the dogmatic consensus of ignoring what was not accepted by orthodox science. As a matter of fact the principles prevailed and persisted as a more or less inarticulate attitude of a growing number of workers and thinkers.

At any rate, Bernard Sachs or anyone coming with the European training who had to enter the ranks of neurology and psychiatry would have had an opportunity to use considerable freedom in organizing his perspective and goal. One cannot help indulging in wondering what we would have mutually found if we had crossed the ocean on the same steamer. To Sachs, of course, it was a re-

turn to his own family and family setting, and undoubtedly to many more or less prearranged connections and anticipations. As I review the persons within the special field I am very much impressed by the circumstantial character rather than any persistent basic drive that seems to have determined the course and form of specialty that shaped itself with them. There were men in whom the views in the field and basic principles had no doubt taken definite shape so as to become lasting determiners, but just as there is a wide difference between planning and actual realization of any career, so it would be possible only through an intimate contact to reconstruct the share of intention and of opportunity. In this particular case I should like to know more about many points but especially the relation with Seguin who probably played a role in many young pupils of his and also in Sachs. I cannot suppress the mention of the example of one of our most prominent men, Dr. William H. Welch. His unusual memory and capacity of organization brought him the prize Seguin annually gave to the one who would give the best statement of his neurological course. The prize consisted in a microscope and with that went the desire to get training where there was a use for the instrument. Dr. Welch decided to go abroad to get his training for neurology. He wanted to study with Heubner whose work on arteriosclerosis of the brain evidently figured to him as neurology. When he arrived abroad Heubner had obtained a chair in pediatrics. Welch turned to pathology and was to study with Wagner who also was promptly promoted to a chair of internal medicine. He therefore drifted very naturally for him in the direction of Ludwig's physiological laboratory and from there was urged to join Cohnheim instead of Virchow, which had no doubt a great influence in the development toward experimental medicine. Of neurology there was no trace of interest. There also was at that time a deep change in Seguin's own plans of life and I should like to know how the organization of Sachs' start arranged itself later. I know that Sachs was much appreciated for his helpfulness in neurological diagnosis to the surgeon Arpad G. C. Gerster. There must have been from the start an affiliation with Seguin's *Archives of Medicine* and the *Journal of Nervous and Mental Disease* of which he became co-editor and from 1886 to 1891, editor. I cannot help regretting that through an accident of circumstances our plan for reminiscing was thwarted; instead of mere inferences one would like to get from the source the links and personal materials in that leisurely manner which should be the privilege of our period of life, namely the conjoint contemplation of the leading preoccupations and their bearing during the formative years of entrance upon actual professional work and their fate. There is so much in the interweaving of plans and of chance that welds itself into the actual pattern, and the yearning for concreteness amounts to a sense of necessity for any truly historical understanding such as this paper aims at. I still hope there may be amends.

In the extensive bibliography published in Tilney and Jelliffe's Semi-Centennial Volume of the American Neurological Association (1924) Sachs had a considerable number of early papers in the field of electro-diagnosis and electrotherapy and apparatus and theory, such as constituted an important part of

the equipment of any beginner at that period, but there are particularly two excellent and fascinating reviews of genuine interest to our subject, because both of these topics played a role also in the writer's own development and in lines of thought of the time.

The first one is a comprehensive statement of Theodor Meynert's *Psychiatrie* that must have had a real influence in the direction of Sachs' thought, or we might put it differently—may have given a striking expression to an already prevailing tendency. This must be so all the more because Sachs actually decided to present an English translation of this unusual programmatic work. Its leading ambition was that of presenting a radical departure from the existing literature in aiming to present psychiatry under the concept of the "diseases of the forebrain."

The second review that came a year later, in 1885, is that of a small book on the *Nature of Mind and Human Automatism* by a young contemporary of Dr. Sachs, Dr. Morton Prince, who from his Harvard days was deeply interested in the development of fundamental conceptions that became the basis of an outstanding system of psychopathological conceptions and investigations. Sachs could not have chanced upon more distinctive and illuminating mutually supplementing topics to throw a light on leading factors and interests: The first one, facing directly the relation between psychiatry and neurology and the second giving definition of orientation and of material to psychopathology along provocative lines testing the very mettle of the reviewer's thought and tendency.

THE MEYNERT REVIEW

In the journal edited by E. C. Seguin, the *Archives of Medicine*, Vol. 12, August 1884, Sachs offered his conscientious and informing six-page outline of Meynert's *Psychiatrie: Klinik der Erkrankungen des Vorderhirns, begründet auf dessen Bau, Leistungen und Ernährung.* In his very sympathetic and really solid summary Sachs praises Meynert's wisdom and courage in his venture to explain the various forms of insanity on anatomical and physiological (and Sachs adds also "biological") data, once for all to be seen as "diseases of the forebrain."

Meynert, with his "extraordinary knowledge of the structure of the brain" applied "to the study of the physiological and morbid conditions of that organ," offers "a new line of research in the study of the origin and nature of mental diseases," since no one before has ventured on an explanation of the various forms of insanity based upon anatomical and physiological data in detail—certainly not so exclusively of the brain, and even more definitely of the forebrain. Meynert is unafraid to make his "every effort to lift the curtain from the mysteries of mind," although others considered this premature and imprudent. "He thinks there is *no need of leaving it to posterity to make deductions from anatomical and physiological discoveries which we have made.* New facts should be utilized at once. Mistakes are inevitable, but succeeding investigators will profit by them." Sachs himself is somewhat wary, but more of haste than of basic risk.

As early as 1876 Professor Meynert introduced his *Skizzen über Umfang und*

wissenschaftliche Anordnung der Klinischen Psychiatrie, with a plan and obligation to put his knowledge of the structure of the brain to definite use, and to follow for psychiatry the brilliant determination of the Vienna school to base the clinical teaching definitely upon the knowledge of its structural foundations. He was insistent to speak radically of psychiatry as "the Clinical Teaching of the Diseases of the Forebrain and its Complications."

"To this effort I was impelled by the conviction that there was need of a *scientific* treatise on mental diseases, in spite of the present large literature on the subject. The least doubt as to the correctness of any views expounded in this book induced me to stop, and to interrupt work until I had satisfied myself of the correctness of those views of scientific investigation and reflection. This will explain why so many years have elapsed from the time the book was begun (1877) to the date of its publication." (p. 6 of the text).

Meynert evidently started to lay down the long one hundred and twenty-five page chapter on the anatomical foundations, and the seventy-five pages on functions, and sixty-four pages on what he calls the 'nutrition,' and an appendix of twelve pages on physiognomics, with its lawfulness in freedom, but didn't bring himself to the publication till 1884, when his publisher gave out the first 288 pages, breaking off at the end of the eighteenth sheet in the midst of a sentence in the first chapter of the actual clinical part. The main purpose of the work is stated to be that of attaining a "natural system of classification" in terms of Diseases of the Forebrain including the cortex and the striatum and globus pallidus, with the thalamus and midbrain and other structures of the brain stem combined in the control of the forebrain.

In 1890 Meynert published a volume of *Clinical Lectures on Psychiatry on Scientific Foundations*, which he says is in no way intended to take the place of the continuation of the first volume which was to be published true to the original intent, but which actually did not come to execution.

It was what Meynert himself called the introductory half of the *Psychiatrie* that Sachs reviewed in a statement I should like to see republished in full, inasmuch as it culls out the essential data and the development of the principles, leaving out, however, in the translation, the last chapter, actually the summary of the introduction and its climax, leading over to the *Klinik der Vorderhirn Krankheiten*, that is to say, the presentation of the essential and fundamental material and proof of his basic conception and goal, the actual clinical observations and studies.

In the presentation of the anatomical part, he was determined to extend his knowledge of the minute anatomy and interdependencies of the parts, and their relation to pathological craniology and attention to the theory of predisposition and heredity, heeding especially Weissmann's dictum, (p. 8) "Talents do not depend upon the possession of any special portion of the brain; there is nothing simple about them, but they are combinations of many and widely different psychical faculties."

Throughout his work Meynert had been keenly interested not merely in a very detailed presentation of the macroscopic and microscopic data of his ex-

tensive studies of animal as well as human brains, with keen attention to the possible hints concerning the functional interpretations and evaluations that could be derived from the variations of the structures. He did not shy off from the privilege and responsibility of the scientist to draw conclusions which took very definite form in conceptions specific to him, and reached freely into psychological and evolutional speculation.

Dr. Sachs writes as follows:

"Whether we consider the cerebral structure from an anatomical, physiological or biological point of view, we must, according to Meynert, distinguish between the cortex and the sub-cortical ganglia; we must remember that the cortex is the one surface upon which all the impressions from the body and the outer world are registered, and that the subcortical ganglia are the way stations, as it were, through which the peripheral nerve-tracts pass on their journey to the cortex.

"The division of these nerve-tracts into projection-systems is too well known to be more than alluded to here. The other (intracortical) system of fibres—the association-system—plays an important role in the physiological and later sections of the book. . . . Meynert has deprived cerebral anatomy of much of the mystery which once attended it." (pp. 88-89).

Dr. Sachs draws attention to the fact that the anatomical part was not kept up-to-date, and Meynert himself speaks in his Preface of important work he had added with the resumption of his old cleavage (Abfaserung) method, and the further development of his valuable collection of microscopic series, to be incorporated in an appendix to the work,—"wherein my views have been necessarily modified or supplemented by the investigations of other authors and my latest researches"—the most important results being those "in regard to the cortical and ganglionic fibres of origin of the *pes pedunculi* (crusta), and the connection of these fibres with the pyramids" and also "the newer work on craniology."

One has to remember that with his keen interest in the comparative anatomy of particularly outstanding contrasts of animals, such as the kangaroo, the bat, the mole among others, there was attention not only to the form but to the uses of the parts, such as, for instance, the correlation of the olfactory apparatus and the differences between the animals whose head was close to the ground with a strong development of the olfactory opportunity as well as utilization, in contrast to those that depend more on vision, and, in man, on the upright position and the use of the hands and a corresponding distance from the ground with a lesser development and use of the olfactory organ. From the point of view of brain anatomy and function, Meynert was one of the first to recognize that the cerebral cortex had not only particular developments of the fibre-systems, but also local differences of structure. The most important feature for the conceptions related to psychiatry is, as Dr. Sachs points out, the cortex-subcortex relationship.

Meynert has very definite views, that he likes to compare with such fundamental laws as Bell's distinction of the ventral spinal roots as motor and the dorsal ones as sensory, or Johannes Müller's conception of the "specific energies"

of the nerve fibres. The latter view Meynert considered unwarranted—the functions being determined by the organs supplied by the nerves; but for the *cortex* he specifically demands the *law* of "*capacity for sensitiveness*" in distinction to sensitivity itself. The functions of the cortex were considered definitely intellectual and completely devoid of either actual sensory or motor feeling, which, necessarily, came into action only as sensation and motility in connection with the subcortical mechanisms. The share of the subcortical functions was, therefore, one of activation, and it was only through subcortical stimulation of activity that actual sensations, motility and especially also their hallucinations could be developed, conjointly by cortex and subcortex.

Meynert's fundamental division of the fibers of the cortex into those of the projection system and the association system receives a supplement. The projection systems, *afferent* and *efferent* for the distinctive sensory and motor fields, he described in 1869 under the heading of the double origin of the spinal marrow or cord from the cerebrum—as Meynert made a fundamental distinction with the pyramidal system serving the voluntary apparatus and the tegmental projection system serving the involuntary controls.

As the *third type* of innervation Meynert had come to emphasize that which he designates as *individuality* (in the sense of indivisible) denoting the *basic drives* and related to a "striatum intermedium."

The pyramidal system was more developed in the animals of higher brain type, and the tegmental more fundamental for automatic activities. Much importance was attributed to the hemisphere ganglia (striatum and pallidum) and to the thalamus as the principal origin of the tegmental system. The cortical memory is purely "symbolic," whereas the thalamus is the station of the actual innervation feelings.

For the explanation of the mental correlations Meynert uses the example of the impression made on the tabula rasa of the infant's cortex by a bleating lamb. The visual and the auditory systems each have their afferent systems for their respective memory symbols, and the two, through the association fibers, are set in a binding association. Such association, once formed, is a permanent one, and of the these images cannot be excited without recalling the memory of the other. If the one gets active, the two will act together for the total presentation.

He gives a drawing of the child with a finger exposed to the flame, and he recognizes the visual memory, the pain memory, and the memory of the motor innervation.

Intelligence is the activity of the entire cortex or the cortex as a unit, and that in turn becomes the basis for logical reasoning. Particular attention is given to the feelings of aggression and the defense provisions, and the affect of pleasure and displeasure, and the regulation of the chemical processes. Sachs points out the aggressive and repulsive functions and the pleasurable and painful emotions as most directly essential in their bearing upon mental diseases. Consciousness, when present, recognizes the inhibition as painful sensation. With repulsive movements there goes a contraction of the blood vessels of the spinal cord segment, through which the sensory irritation passes—with the dyspnoetic

phase of the nutrition of the nervous elements, while the pleasant arousals, as in Goltz's croaking experiment, with very slight stroking between the shoulder blades of the decerebrate frog, goes with a functional hyperemia. Moreover a memory of a former pain or pleasure will be sufficient to cause the corresponding concomitant states. The support of the entire function is based upon and described as "nutrition," a chapter full of interesting questions.

In this frame Meynert gives the material with which to do justice to the possibility of understanding mental disorders as actually referable directly to the forebrain mechanisms. The main weight rests no doubt, as Sachs realized, on the passing of the peripheral nerve tracts through the sub-cortical "way-stations" and reaching the cortex which is otherwise purified of all sensory and motor taint, serving the symbolic pure culture, intelligence.

The following direct quotation from Dr. Sachs' review gives a good picture of samples, many of which are plain instances of neurologizing tautologies, putting in neurologizing terms what only suppositions make one suspect.

> In functional disorders the first effect "of a change toward defective nutrition of the cortex is a loss of cortical inhibition; as soon as this inhibitory force is removed the play of the subcortical centres begins; hallucinations and deliria are the result. *Irritation* of the subcortical centres may bring about the same result, while a *weakening* of the subcortical functions produces an increase of cortical power. Meynert explains this in the following way: Supposing that general anemia of the brain has produced exhaustion of the hemispheres and of the subcortical vaso-motor centers, then a paretic condition of the arterial muscular walls will ensue, and the result is hyperemia of the cortex. As long as the condition lasts we get a full complement of maniacal symptoms, viz.: pleasurable mood, an abundance of loosely associated ideas and innumerable motor impulses. By finally causing an arterial hyperemia in the vaso-motor centre itself this condition works out its own salvation; the vessels of the cortex contract normally again, and the maniacal symptoms disappear. If this process (of vaso-motor irritation) is carried to the extreme the contraction of the cerebral vessels will become more intense, and all the symptoms of a melancholic mood will be developed" (p. 92).
>
> "Irritation of the cortex could never produce anything but abnormalities of thought—insane ideas—and pathological emotions; but the latter have been shown to be mere intensified perceptions . . . that insane ideas are never newly formed, simply reproduce such primitive ideas as a child possesses that has no proper appreciation of the relation of its own individuality to the surrounding world. The exaggerated or otherwise defective notions of the normal child are limited and corrected by experience" (p. 92).

It is well to bear in mind that these comparisons of clinical facts and forebrain postulates appear on the background of the last chapter, perhaps the most vulnerable, and omitted, or rather deferred in Sachs' translation.

Meynert likes to think of the peripheral nerves as if they were projections of an amoeba or octopus, drawing in the outside world into the self. He presents the human being for his special organs and emphasizes those two particular all-pervading systems that give him the "vascular system man" and "the nervous system man," so familiar in old anatomical pictures; and how, within that, the proportion of development of the heart and vascular system and the central nervous system and its all-pervading ramifications come to form a challenge for comparisons. The relation of the vascular control and the lowering or

raising of the mood becomes one of the constitutional as well as temporary factors of importance. In addition to this balance or imbalance there comes the element of cortical inhibition, and, on the other hand, the emphasis on "localized irritable weakness." He emphasizes the orientation of the child as seeing all things in relation largely to the self. In keeping with that go so many things, harmless in the child, such as the tendency to fear strange men, and, in the antique world, an equivalent of great wealth of chances for animisms and for what in the adult would rank as delusions. There further figures the psychic hyperesthesia with anger, and the relation to innervation feelings, inhibition, confusion, inconsiderate destruction, defecation and urination, as in epileptoid states, anger outbursts, and subcortical irradiations, such as anxiety with confused defense, and visceral involvements; and on the other hand, the hysterical symptom complexes, the hyperesthesias and anesthesias and reflectory irradiations.

Considerable attention is given to the confusion factor, the exaltations, the persecutions and the content of hallucinations, and the relation of the whole to volition, the sense of freedom, the sense of compulsion, the psychic hallucinations, the condition of partial waking states, and the modifications of a toxic character. Illusions are said to be by no means very different from delusions.

With this general type of consideration, Meynert offers the grouping which deserves being presented as a preliminary indication of how the ambition of the clinician will turn either in the direction of the challenge of Meynert or raise the question of whether our knowledge of the forebrain and its function can become an adequate substitute for what might well have to be a natural history, and at the same time humanly intelligible and therapeutically useful and important treatment, in one term or another, of person-function.

A comparison of the anatomical fundamentals and of the table and how they could take the place of the clinical pictures leaves an uncomfortable feeling about the material the student and physician would be expected to work with. We are perhaps unduly verbal in our records and inclined to use specific statements *ad hoc*. The old blanks for checking off standard items might make one feel more confident and hopeful and satisfied. Sachs' hesitation about including Meynert's blue-print in his translation is probably the best indication of his reaction.

It isn't to be expected that Sachs took too seriously those deficiencies which he felt, so that they would have diverted *him* to a more searching type of demands in psychiatry, in the direction of avoiding a mutual bolstering up of anatomy by the clinic and the clinic by anatomy. But it seems fair to those who only have the English translation, to get some reasons for the precautionary reluctance, if such is one of the causes of the omission of the final chapter, by having an opportunity to get Meynert's skeleton of what the clinical part was going to prove, and to envisage his correlations.

A. Anatomical changes

I. Malformations of the skull and brain through intrauterine, intrapartum and infantile processes or events.

Clinical pictures: Predispositions, cretinism, idiotism, deafmutism.

II. Focal Anatomical Processes of the brain, hemorrhages, softenings, tumors, gray sclerosis, syphilis.
Clinical pictures: Deliria, palsies, localized dementia, traumatic confusion, symptomatic chorea and disposition through residuals of such processes.

III. Diffuse anatomical processes of the brain and its membranes, hypertrophy of the brain, atrophy of the brain, acquired hydrocephalus, meningitides.
Clinical pictures: predispositions, dementia, paralytic dementia, senile dementia, deliria, basal meningitis, acute (fatal) processes with chorea, hysteria, epilepsy; senile processes.

B. Nutritional disorders

I. Cortical irritative processes.
a. Irritable mood, disposition. Pure maniacal excitement.
b. Simple melancholia, depressive mood with inhibition self-depreciative and self-accusatory delusional states.
c. Simple mania: Elated mood, flight of ideas, flight of motility and megalomania. Supplement: Chorea.

II. a. Irritable states of subcortical sensory centers. General delusional states. Simple hallucinatory confusion. Compound hallucinatory confusion with stuporous and manic periods or developments.
b. Irritable states of subcortical sensory and common feeling or coenesthesic centers. Hypochondriasis. Hysteria.
Partial delusional states: delusions of being noticed; persecuted; megalomania.
Annex
c. Disorders of the subcortical vascular centers and hyperesthesia. Epilepsy, Hystero-epilepsy
Exhaustibility
Circular psychoses of melancholia, mania and lucid intervals.
Annex: Paralyses. Ascending paralysis. Graves' Disease

C. Intoxications

There is no doubt that Meynert is one of those figures in the history of psychiatry which come closest to being ranked among the geniuses. He himself characterizes genius as "the one with a smaller tendency to error in thought and conjecture." With his wealth of capacity for correlation and the intensity of his pursuit of the particular techniques in the study of the brain, he combines most of the features that in his younger years made him what today would be called a problem, but also a poet.

Meynert was the son of a singer and of a historian, and had a sister as his historian. After a turbulent and prolonged youth (he was twenty-eight when he graduated in medicine) he made the study of the brain as much part of his real life as he had done with what others would have considered the "distractions" of his student years. (See Anton's account of his revered master in Kirchhoff, Deutsche Irrenaerzte, II, 121–135). He became an arduous worker when he worked, as arduous as when he wrote verse and when he allowed himself freedom of many of the ordinary inhibitions. His fiancée and her father seemed

to be the ones with unfailing confidence in his capacity and ultimate concentration.

Meynert's early studies are *Cerebellar Atrophy*, 1864, thalamus disease, *Speech Disorders*, 1866, *Weights of the Parts*, 1866, and, in 1869, *The Double Origin of the Spinal Cord from the Brain*, and the annual reports of the *Centralblatt* show the progress of his interests.

Meynert belongs to the Vienna School, intent to base its teaching on structure, but with free range of vision. He expresses it well in one of his verses:

"Ich will Gedanken in die Leichen säen
und vieler Geister Brot soll draus entstehen."

and it is also written: "Anatomy may not give us a psychiatry, but much of the progress of Vienna has come from the cemetery."

Meynert's *Psychiatrie* was one of the most intriguing and ambitious proposals of the time, a study of the brain by a highly temperamental investigator, combining a differential study of the *cerebral cortex* and the gross study of the *projection and association fibers*, (partly in sections, and partly by splitting the hardened brain in a macroscopic pulling apart of the fiber systems) in microscopic and comparative study of the mammalian brain, largely of the carmine sections of higher mammals and man—and all this in the midst of his clinical responsibilities and teaching. It is interesting to compare this product of brain anatomy (conceived as "the foundations of a Psychiatry" as introduction to the "Klinik" of the Diseases of the "Vorderhirn") with the contemporaneous works of Reichhardt and Schwalbe, and especially the *Lectures* of L. Edinger that appeared a year later, and the older monographic work of Forel, who wrote his thesis (1872) on the thalamus under Meynert, but his classical study of the brain stem, or Haubenbahnen, 1876, while assistant of von Gudden, highly critical of Meynert.

In his final (deferred) chapter of the general part Meynert repeats the urge for a "natural classification" of the mental diseases, the fundamental claim of the preface; but he also draws attention abruptly to the fact referred to above, that the content of the forebrain performances should *not* be called *memory image*, but *memory sign*. He says this "sign" is *as far from the sensory "image" as the algebraic sign is from the object* to which it is related, (reminding one of what prevails in different sets of integrates attending to their own respective business). It is in this sense that he can speak of forebrain function as "mental," in the sense of intelligence, and of its morbid disorders as "mental diseases." But for the live and active and concretely telling life, Meynert looks to the collaboration of the subcortex. Whatever contains a really sensory component and motion or action shows not only the origin but receptivity to influence from the brain stem. He looks to the actual contributor of what is needed for the occurrences of feeling and action and of objective evidences of emotions and the reflex-mechanism, but also what gives real or false conviction of reality, in hallucinations and delusions. In keeping with this, the "stem" is separated in the "Meynert dissection" from the cortex, and includes the globus pallidus, striatum and the thalamus to permit of meaningful comparative weighing—too simple a method for a field with far too great a complexity of differentiation.

It cannot be mere chance that the inspiration Meynert had in 1876, and that took eight years before producing the fragment, could not have had some connection with intrinsic difficulties which he himself must have labored under or been conscious of. The same inhibition suggests itself in the attitude of Dr. Sachs, who hesitated to expose the author to the premature presentation of this final chapter of the general part of the book, lest it would lead to premature adverse judgment.

It must have been a great event for Sachs to meet Meynert at the period when he tried to get square with a natural classification of the most obstreperous material of form and content and growth and change, tempting and defying. Bernard Sachs' steady temperament was necessary to give Meynert a translator capable of recognition of the spirit and ambition of the master. It must be said that the translation is remarkably faithful and accurate.

In the absence of clinical contributions to psychiatry there is no material by which to test the question whether in Sachs' later work attempts at using the forebrain as a basic background became any dominant preference. Certainly in those statements to be mentioned later, Sachs remains on a very sound common sense ground, referring special clinical facts to the broader clinical setting as most of us are doing, rather than to "the forebrain."

That there have been interesting attempts that would belong to the hoped-for Meynertian forebrain psychiatry can be seen in the Vienna school, particularly in Schilder's and Hoff's studies of the forebrain symptoms in schizophrenia. But the present day contributions of the importance of thalamic influences are undoubtedly based more on real experimental work than on constructive hypothetical illustrations.

Meynert represents important facets and is one of the potentially perplexing but significant influences in our field. He came to play an important role for many of us, and, to Bernard Sachs, he no doubt constituted a great deal of a differential influence at a formative period. The work and time spent on the translation was not time lost. Historians will have to do justice to Meynert if they do not want to make grave errors. Wernicke and Anton and ever so many others could not easily be correctly understood without an accurate following up of the master's intentions and suggestions and effects.

Meynert worked in a period of transition, passing from "speculative science" to demands for strict observation also in the field of subjective life, something which even to this day is rarely understood and practiced as soon as one comes to man and his function. Perhaps our times have gone to the other extreme. There is frequently the erroneous idea that unless one could use tracings and mathematical translations of the facts, the data and statements could not be taken as up to standard. Unless scientific method of *presentation* is used, scientific procedure even with conscientiousness of observation and recording is apt to be unrecognized as such, and also too often not practiced. This is the tragedy resulting from a great deal of the medical training and medical expression and medical accuracy of form with slight sense of responsibility for the verbal statement. It is interesting to see how little reliance is put on the best way of statement of many psychiatric observations in terms of history, which,

if dependable, frequently gives otherwise complex events the closest and most meaningful and useful formulation, which would also express in the most natural way the setting in *treatment* as "history in the making." It is one of the drawbacks to the simplicity of formulation that so many important psychobiological data are actually correctly expressed in everyday language and thought and appreciation of relations, the scientific validity of which academic science is not accustomed to accept. As long as mentality and language are not adequately studied and rated as *meaning-function* we shall be forced to make sure whether the user of language is operating with scientific conscience in the use of plain and critically dependable language. This is one of the most constant difficulties psychiatry has to contend with. We must find ways to make ourselves trustworthy by practice. A perfectly good check on a perfectly good bank cannot be evaluated by anyone who does not know the deposit.

For some time to come I trust more and more adequately, the great responsibility of psychiatry will be to debunk language irresponsibly used and irresponsibly taken. The practical test of Meynert's attempts to attain his ideal and the "natural classification" will depend on one's devising methods of recording and the use of language which does not draw most of its authoritativeness from the semblance of its belonging to systematizations of solid theories and acceptance of dogmatic and popularized generalizations. We need expressive words for plain facts.

Merely speaking in terms of anatomy, histology, products of current scientific attempts and practice, does not make science. Anatomy does not immediately make psychiatry; physiology does not necessarily give us evidence that its data actually belong to the reasoning or problem on hand.

What is the principle of psychiatry? That it works "*psychologically*," by *symbolization* and *meaning*—as Meynert seems to imply in what he reserves for the cortex? He seems to be close to the fact of mentation or symbolization and subject-function, or developing cortex and cortex function, and a medium of a special system that serves a time-using process with differentiation, but also a hanging together and operating system. To Meynert the cortex is the reflector of the outside world and the subcortex the regulator of vascularity and nutrition or circulation. But what is the material and what the regulating principle?

Does the form of the structure do what Meynert quotes Lange to see: "the maximal advantage of a really illuminating, clearly order-producing morphology lies in the fact that it opens a direct insight also into the function?"[2] Unfortunately Meynert's "morphology" is not factual enough to do this.

In July 1885, Dr. Sachs, then Conjoint Editor of the *Journal of Nervous and Mental Disease*, presented an interesting review, which leads as deeply into definition of concepts as did the other in the direction of broader correlations. The highly complex structure of the brain as organ after all is a product of heredity and growth, and its use is the service of life function of the organism as individual and member of a group. To find the pivots of control and common

[2] Quotation from p. 94 of the *Klinische Vorlesungen über Psychiatrie auf Wissenschaftlichen Grundlagen*, in the discourse of *Psychiatry and Jurisdiction*.

principles is far from attained. A great deal has been gained from the Meynert concept; but the "natural classification" was badly chosen, the facts are not clear. Whether we think and work in terms of the nervous system or of the "person-function," we have to meet both of these, but certainly the one of how to guide and use the "person-function" and "the mind" or what the term stood and stands for, must be clarified first.

We enter then upon *the second find of an interesting topic*, which, in a way, supplements the far-flung dream or venture of Meynert, and brings up the necessity of what it is the would-be psychiatrist has to square himself with in detailed definition and characterization. Part of this is the task of overcoming the rigidity of the scientific dogma, according to which daily life has to be kept out of strict science both in the cultural and the natural science domain. Just as in the development of the novel it took a long time before the ordinary individual and the simple situations received attention, so the respect for what is solid in the ways of conducting ordinary life was late in gaining the respect of the academic gowns, cultivating generality and the equivalent of "laws of nature." Dr. Prince evidently started as a well-trained wrangler and essayist in the best sense of the word. In the one hundred and seventy-page book to be discussed he was equal in form to Fiske and Spencer and Clifford, his fellow "Noumenologist," and speaking in terms of the absolute subjectivist. If we are to give an example of keeping the facts of man in sharable form before us to carry the sense of what all humans should be able to participate in and with, we want to see that it receive the expression serviceable in health and disease, and intelligible and workable for all.

THE MORTON PRINCE REVIEW

With the second review mentioned, Bernard Sachs had an opportunity to come closer to the more intimate problem of not only psychiatry, but all human functioning of the mentally integrated type. It may, of course, have appeared justified not to take sides on such a fundamental question as the attempt to dispose of the problem of the Nature of Mind and Human Automatism, but, after all, that book did not occupy itself as much with the creation of it all, but with an understanding of the actual working principles.

The conservative but keen review of Morton Prince's *The Nature of Mind and Human Automatism* (July, 1885, *Journal of Nervous and Mental Disease*) is the other postgraduate pronouncement of Bernard Sachs. It marks perhaps a caution rather than eagerness to develop any lingering preferences for his own collegiate premedical interest in the mind and mental disease, with a sense of the mind-body problem still a "mystery," rather than a sphere of accurate and profitable work. A warning against too deep involvement is suggested by the manner in which the review begins.

"We shudder to think of the task Dr. Prince has set himself in the little book before us; and we stand in awe of his courage when we read that this task was first attempted in a graduation thesis 'some eight or nine years ago' . . . Dr. Prince has done well, however, in rescuing from utter oblivion his essay on the relation of mind and matter—that mystery of

mysteries, which has baffled the ingenuity of the ablest minds of all ages . . . 'usually deepened by a dust of their own raising', with the chief difficulty not so much, so the author would have us believe, in the problem itself, but in the cloudy notions which some of our modern gods—Spencer, Tyndall, Huxley, Bain and John Fiske—had of *what* had to be solved. To state the problem clearly is to give half the proof. What *is* and what is *not* to be discussed was perhaps never brought home to our minds as vividly as after reading this essay. But how about the other half of the mystery? If he has not explained away the mystery altogether, he has, at least, defined most accurately the exact nature of the problem to be solved."

Sachs goes on to say, "Prince concedes very justly that we have mental and physical 'phenomena' to deal with." Prince actually says, p. 8, "Today the weight of authority is in favor of a material basis for all mental phenomena, and it is conceded that mind depends upon the development of a peculiar matter, the brain, for its existence." He does not speak of *function*, but insistently of one *substance*, mind. The mental phenomena (our own) we know directly as thought, sensation and emotion (such as pain or thirst); the physical phenomena, utterly unknown objectively are represented by "symbols in consciousness." One would surmise from that that we might deal with a thoroughgoing introspectionist or Berkeleyan.

Trouble comes from raising the question of how is consciousness formed, (and how it operates) and that is where Prince opens the door to perplexity by introducing the objective data, as "undulations (in the nervous tissue) reported as apprehended by another person." He considers four possible hypotheses concerning consciousness: the comparison with some kind of secretion; the parallelistic non-dynamic concomitance (the steam-whistle theory of Huxley), which allows of no dynamic influence of the consciousness elements in the actual running of the "machine;" or an appeal to some ether theory; or Prince's own theory, as follows:

"Consciousness (as made up of the directly known subjective, and the symbols of the 'objective unknown') may be a change in the mutual relations of the *actual* or *real* molecules of the protoplasm of the brain-cells: that is, *these unknown physical disturbances themselves—into protoplasmic disturbances as they really are: the actuality of so-called neural undulations.*" (p. 50)

And again it is stated:

"The former (the mental state, such as pain) is the actuality, the latter (the physical changes) a mode by which it (the physical condition) is represented (in symbols for the objective terms) to the consciousness of a second person, i.e. to the non-possessor of it" (p. 55)—in other words, what the observer adds as objective data to the subjective feeling of the sufferer.

From another place Sachs quotes:

"Instead of there being *one substance with two properties or 'aspects' there is but one substance*—mind, (i.e. the subject's direct realization or content), and the other *apparent* 'property,' viz. motion, is only the way in which this real substance, mind, is *apprehended by a second organism* (in the sensory symbols or mental pictures aroused for the physical events objectively observed by one who does not have the pain, but the sensory symbol report of what goes on as molecular motion)." It is all mind, therefore, and nothing more, so he says.

If so, the author would indeed be justified in saying, as he does (p. 37), that "a great deal of thought has been devoted to trying to understand how molecular changes are transformed into consciousness, when in reality there is no transformation at all." And yet, though we call in the agency of a second organism we still have to cope with two sets of facts. Call them mind and motion, different properties of mind, or different properties of matter—call them what you will, the exact relations of these two different facts remain the chief mystery. (Sachs' other half of the mystery?) To the extreme subjectivist the objects are bundles of sensations, the *symbols* of the objective world, and therefore, also material of consciousness, while the pain is directly felt as an immediate organismal response. Obviously mere fragments of the ninety pages of close reasoning after the best manner of the essayists of his time—Fiske, Spencer, etc.—cannot easily be condensed into a few sentences. But with the definitions given and actually used, the argument is rigidly carried—even if in the end it might be using definitions in a circle.

Sachs reviews the successive chapters of the book, and points out how, in the discussion of reflex and automatism and materialism, self-determination shows itself with *actual positive influence by consciousness*, or, at any rate by the pain in the consciousness. This is indeed the somewhat hidden, but yet effective essence of Prince's stand. Sachs asks—"But now comes the rub. How is it that one state of consciousness is perceived as another state of consciousness (in a second person)? On this point the author argues very acutely, and fortifies his position by the use of concrete examples. These are most happily chosen, and it would be doing the writer an injustice to quote them here apart from their context. . . . Dr. Prince thinks man an automaton, but not an automatic machine. And he shows that the reflex actions of man are largely subject to the influence of consciousness. Like all writers on automatism, our author sees the necessity of discussing the bearings of his theory upon free-will. In the section of Self-Determination he argues that freedom of the will is compatible with his theory of the reflex character of our ideas. There is a final chapter on Materialism" illustrated by anthropology and criminology, and closing with resignation: "Man, like the brute, can only be tamed and morally educated by the alternate use of sweetmeats and the lash!"

Sachs praises the cleverness and clearness and the originality, but after all, sees the main value in stimulating the reader to *reanalyze* his *own* views: and he hopes "that Dr. Prince will ultimately turn his attention to the study of mind in disease, to those questions in particular which are on the borderland between psychiatry and psychology. Few medical authors would seem to be better qualified for this sort of inquiry"—evidently a polite dismissal with a compliment.

Sachs does not state his own "reanalysis." Nor does he single out what, in this case, is and is not to be discussed. The body-mind problem is something intriguing and variously handled or shunned—producing a longing for something better than indifference, or appearing as something to be avoided as hopeless, because it may lead nowhere, and may fail to arrive at any point of satisfaction

or ease or composure and profitable solution? There is the question, how the topic and its handling is likely to affect one's attitude and procedure in the choice of psychiatry or neurology.

To me the review and its material is of special interest because this book is the forerunner of what became one of the productive developments in Prince's career and active work, presented in *Dissociation of Personality* and *The Unconscious*, not so much as psychiatry, but as shaping his own psychology and psychopathology. A further reason for my interest is more personal. At the same stage of preparation for my own work in neurology, on my return from London to Zürich for my thesis work, I came across a paper of the same Morton Prince, in the Summer part of Brain, Vol. 14, 1891, giving a similar, though in a way simpler formulation, that lingered with me as a problem somewhat miscarried and in need of reformulation. I never could help encouraging my pupils to consider it their concern to be reasonably clear about their own body-mind orientation, and not to think in terms of mystery. To follow the good principles recommended by Sachs I reread the 1891 article and the book, which I never had seen before, and found in the same number with the review, July 1885, another interesting presentation of Prince's standpoint, given to the Massachusetts Medical Society, on *How A Lesion of the Brain results in that Disturbance of Consciousness known as Sensory Aphasia.* These papers and his clash the same year with Professor Dwight on the "vital principle" show more concretely what Prince wanted to discuss and what he intended to leave with and for the readers, concerning what there was to discuss and what not to discuss.

In the 1891 paper on *Hughlings-Jackson on the Connection between the Mind and the Brain*, Morton Prince challenged Jackson and his pupil Mercier, a keen British psychiatrist, for their sharp differentiation of the psychical from the physical, and their dogmatic belief that volition ideas and emotions could not produce movements or any other physical states, but would be as completely without power of modifying that working as the steam-whistle of an engine. Yet, if under the influence of anger Prince strikes a man, his anger is not a mere steam whistle. What is the relation between the anger and the physical action? They are not two different facts, but form one fact of common experience, not a parallelism or different "aspects" of one and the same underlying "thing." He repeats the same argument and formulation given in his book. "The reality of the cerebral molecules and motion are only the modes by which *one* person apprehends *another's* conscious states. Consciousness is not correlated with molecular motion in the same individual, but only with states of consciousness (i.e., the mental pictures of molecular motion) in another person." The "reality" of an actual pain *I* may have as parallel, or better concomitant with, the picture *you* may have as the symbol in *your* consciousness of the pain process in *me*, is, objectively viewed, actually the "thing-in-itself" of my pain as an item of both structural and social persistence. This is what his Berkeleyanism leads him to.

The main point of harmony between Prince and myself is his break with the concept of an inert rigid parallelism, which amounted to a denial of dynamic effectiveness of the "mental" functions. The necessity of recognizing the potency of mentality seems too obvious to one's natural sense and experience, not only

with hypnotism and suggestion, but with all emotional and intellectual and conative function. The denial of this by the adherents of human automatism made William James write: "My conclusion is that to urge Huxley's automaton-theory upon us (and I should say also non-dynamic mentality) as it is now urged, on purely *apriori* and *quasi*-metaphysical grounds, is an unwarrantable impertinence in the present state of psychology." (Vol.1, 138.)

The difference between the reaction of Sachs, and mine in 1891, and with my rereading of the historical material, might be stated to the effect that I could not have argued in terms of volition or of pain with one definition of subjective experience and another definition in terms of molecular motion in the nerves, and symbols in consciousness in another, or the first person with the noumena of realities, but the one person who is the common denominator of the pain situation and process. I should have preferred a trust in the meaning and working of the average human *function*, in terms of *mentally integrated performance*. I actually felt from the start, and in my reading and working, stirred to look for a better solution of the mind problem closer to direct experience and functional understanding, than that it should be declared to be and to remain a mystery, or require some dogmatic "solution," with wholly imaginary superaccuracy of argument and definitions of irrelevant detail. If I studied scales or a balance and the laws of its operation should I talk of the molecules or just look for the items available and necessary for discussion and trial? Scales present the problem of a cross-bar resting on a fulcrum and calling for equal weight on both sides, and not a discussion of molecules. The problem in the anger or pain deals with a biological organism functioning with a system of symbolization, or special state of function linked in a common denominator of function, and not of molecules. After all, we are looking for the explanation of the person's own endowment with consciousness, and its use and not for molecules nor for a second person as M. Prince does.

The real difficulty lies in the fact that most scientists can and do remain dogmatic on traditional terms and concepts with all their implications, and are unwilling to turn to the facts and their relations and to treat them in terms of facts and their methods and trial instead of forcing the facts into non-pertinent terms and concepts. Extremes of materialism and idealism speak promiscuously of "matter" when we deal with specific live entities. Tradition insists on maintaining stipulations favoring what some might like to remain a mystery. The assumption of dogmatic "certainty" is wrongly asserted instead of concepts of genuine relativity and genuine probability of the order of biological entities with specific assets. In speaking of body and mind, a dualism is set up with a sidestepping of the distinctions of structure and various functional relationships, missing thereby the meaning of symbols and symbolization as function, and the meaning of levels of integrates in both the neurological and the psychobiological fields. After all, there is a great tendency to forget that the word *idealism* in philosophy refers to a system of ideas and facts and not primarily to ideals, and that ideas are prototypes of *symbols*. With the basic realities and actualities we shape terms and methods adapted to the facts and events. We see what we find "there" to discuss and work with, and do not discuss what does not belong to the issue, that is the Sachs' principle!

With all his brilliancy in working out and developing his several Misses Beauchamp, and especially the famous Sally, Morton Prince remained one of those who had to start from "something else", from a construct, the "unconscious"; but he also showed the method of its study as *co-consciousness* (in his excellent contribution to the International Congress at the St. Louis World's Fair, 1904) in automatic writing and in waking suggestion as well as hypnosis. At the same time he remained aloof from the Freudian psychoanalytic oversystematizations, which Dr. Sachs himself was later so vigorously at odds with, preferring to leave the solution wholly to less theory-charged practical life.

Prince comes close to the recognition of symbolization (although only for Clifford's "ejects"), and perhaps also to special sets or grades of integrates, but his period was too close to either a body-mind dualism or a spiritual or materialistic monism, with no room as yet for respect for actual function. Prince evidently started from mind as the essence of man and of knowledge, like the "*Cogito ergo sum*," and Berkeleyan subjectivism, with an egocentricity difficult to be assertive about to-day, but at that time swaying Mach and his followers even in physics, as shown by William Kingdon Clifford, Hertz, etc. If even physicists were led into experiments with problematic metaphysics, the inquisitive psychopathologist might want to react against the extreme of elementalism and atomism with an assertion of the *subject* and of *life* as we actually find them.

On this point, the same period, September 10, 1885, brings from Prince's pen a very caustic tilt with the Harvard anatomist, Professor Dwight, who in the June number of the Boston Medical and Surgical Journal criticizes William A. Hammond's denial of a vital principle in his *Relations of the Mind and the Nervous System* in the Popular Science Monthly of November 1884. Prince's book, and his paper and the reply to a reply all point clearly to the distinction of inherent vs. extraneous properties, in the conviction, shared with Clifford and others, that the power manifested throughout the universe distinguished in all matter must be the same power which in ourselves wells up ultimately under the form of consciousness.

This is the sense of the stipulation that what is claimed concerning the molecules and the structure and happenings in the nerve consists in our knowledge only in terms of sensations, that is, data in the consciousness of the observer, whereof Dr. Sachs says with wholesome common sense:

"It doesn't appear to us, however, to simplify matters much to state that the parallelism (as in the case of a sensation of pain and the accompanying physical phenomena) is '*between your consciousness and my* (the second person's) *consciousness of your consciousness*.' "

As we concur with James' attitude, we evidently refuse to split the pain-reaction into a "physical" process and a mental one. We mean to work with the pain and all the subject reacts *with* it.

Prince himself characterizes his attitude as that of "my doctrine of panpsychism" (The Unconscious, p. 130)[3]—which then might be the remedy for pan-

[3] In *The Unconscious* (p. 119), Prince describes his panpsychism and parallelism as follows: We need not here inquire into the nature of the parallelism, whether it is of the nature of dualism, e.g., a parallelism of two different kinds of facts, one psychical and the other physical; or whether it is a monism, i.e., a parallelism of two different aspects of one

materialism? Have your choice or better dismiss the false alternatives. If neither the one nor the other version satisfies the inquiring and conscientious scientist, the way is open to the conception of psychobiology or ergasiology, resting on one principle of "sense *and* action" as ergasia and a frank critical pluralism, with ranges, or steps of special sets of integrates. After all, this description of unity with differentiations is the most tangible statement we can make of the actual state of affairs, treated in terms of objectivity, including subjectivity as it operates in the use of symbolizations—in memory, attitudes and feelings and thoughts and concept formation.

To the usual Occidental mode of thinking, properly acceptable in our scientific conceptions, our description of the data of observation and science can well be given in language which seeks its interpretation and justification not only in a subjective consciousness of the individual, but as the objective expression acceptable to and to be accepted by *any* competent and responsible individual. This is the criterion of objectivity even of subjectivity, which once for all renounces the detached and absolute animism and the hangovers of ghost-lore and tradition-ridden metaphysics. The self referring middle form of the Greek verb *ergajomai* expresses this blending of subjectivity and objectivity.

The indulgence in the intellectual pleasures of argument of that time had its own rules and goals. It matured in Prince into something clever and systematic, but with its start from the subject taken as the center, it was not the fairest and best start for a study of *nature*. He was after the essence and declared as the unknown that which the naturalist would consider the very center of objective study. The extreme stand of the subjectivist will not want to deal with the object directly, but only with the sensory material arrived at—the very reverse of what the naturalist does. The study of Prince was worth while as such, and especially so because it grew into a productive life-work akin to the Janet school, which, however, builds upon the activity-principle. It became, if not "the" American school, certainly the equivalent of the best that could have come out of Beard, and a blossoming out of what Prince laid the foundation for with his intellectual stunt.

SACHS AND PSYCHIATRY

Sachs' relation to psychiatry reached a high point in 1897, when at the Baltimore meeting of the newly rebaptized American Medico-Psychological Association of the somewhat widened group of the Superintendents of Institutions of the Insane, he was invited to be the friendly contributor toward a reestablishment of a less militant factual and fair relationship. It was during the year of Sachs's presidency of the American Neurologocal Association that S. Weir Mitchell had delivered to the State Hospital men of the American Medico-Psychological

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and the same fact, or a parallelism of a single reality (mind) with a mode of apprehending it (matter)—mind and matter in their inner nature being held to be practically one and the same. The theory of memory is unaffected whichever view of the mind-body relation be held." All these assumptions can be made consistent for argument, but the question is whether they concern themselves with what *is* discussed and is *not* to be discussed or *must* not be discussed out of the proper context.

Association his address (*Journal of Nervous and Mental Disease*, July 1894) which might be called unsparing criticism, and a vision of institutional psychiatry from the viewpoint of the neurological and humanitarian angle of the renowned neurologist of the Orthopedic Hospital and the privileged class, the fat and blood and world-travel period of the Philadelphia schools. Mitchell had declined the invitation because he knew that what he would say would be far from pleasing. When the group insisted, he went ahead and wrote what a history might well reprint in full, together with the response of Channing, so as to have a factual rather than merely suggestive and emotional background: a harsh criticism and a utopian picture of a model organization.

The Baltimore address of Bernard Sachs on "Advances in Neurology and their Relation to Psychiatry" (*American Journal of Insanity*, 54: 1, 1897), was a memorable and noteworthy expression of the best thought and training offered at the time, clearly put under its title and true to the title. It deserves to be re-read from time to time as a remarkably broad and comprehensive survey of the beginning of a decade of great neurological and psychiatric activity, with "a fair deal attitude" in matters also of person-function, but in keeping with the title little specific orientation on what the demands on real person-function and clinical psychiatry would be.

Sachs granted his hearers the compliment that

> "No one can be thoroughly devoted to a study of the organic diseases of the brain and of the spinal cord without at the same time taking a deep interest in psychiatry. I have no doubt that others, like myself, would never have entered the ranks of neurologists if they had not been impelled to the study of nervous affections by a special fondness for the analysis of mental conditions. If there be any differences between us, we must concede that you are our superiors, at least etymologically. As psychiatrists you are healers of the soul, while we neurologists are mere students of the nervous system . . . . We neurologists have a speaking acquaintance, as it were, with diseases of the mind and, while we envy you the opportunity that you have of studying the patients and their morbid manifestations through the entire period of disease, we have an occasional advantage over you in seeing the patients in the very earliest period of the disease and in being able to study a goodly number of those who never reach the asylum door."

In contrast to S. Weir Mitchell's impeachment, Bernard Sachs enters upon a conscientious evaluation of the work done and being done in the whole range from structure to function, mentioning as samples the contributions from anatomy to psychology, and speech and morbid psychology, general paresis, paranoia and "acute mania". He gives due and detailed recognition to the post-mortem studies in state and local laboratories and turns to a survey and evaluation of the study of the cortex and localization and a synthetic picture of the work of Charcot, Jackson, Flechsig, Wernicke, Ferrier, Hitzig and Munk and Goltz, with Kussmaul's and other studies on the development of the child from the intrauterine stage on, with the cortex a functional concern up to the association psychology and the progress from Meynert to Wernicke, with wide open gates for a future. It is indeed a very telling and informing picture, doing justice to the products of some of the American workers as well, a picture worthy of perusal today as reflecting in substantial terms the live and active period of the turn of the century up to the preparedness in the first world war. There is a warning against letting

psychology run too far ahead of the anatomical and physiological foundations, a premonition of Sachs' later caution and his condemnation of the interpretative ventures of the postwar spread of analytic trends.

He gave his audience a picture of the work on localization, which led him to the formulation of the *ordinary psychic process* in the following order: "First, peripheral stimulation; second, perception in one or more sensory areas; third, formation of a concept; and lastly, a motor discharge"—allowing Ziehen to maintain "that the association psychology is sufficient" to explain all the experiences of clinical psychiatry, and another still more prominent writer, Wernicke, to express the opinion that the disturbance of the association tracts alone suffices to explain abnormal psychic disturbances. But he insists that catch phrases are particularly dangerous. He turns to Flechsig's work and Edinger's comparative anatomy and to the chronological and phylogenetic development in the optic and visual apparatus (to the understanding of which his teacher Seguin had contributed valuable data) and the auditory pathways and the motor paths—and Flechsig's association centers and the line of further intensive work on the infant's brain, and, in the adult, the study of Kaes, and the neurone concept—throughout with fair and suggestive evaluations.

There remains, of course, the question to what extent the advances in neurology actually play into the problems of psychology and psychiatry and anthroponomy. Clearing up matters of neurology will no doubt prevent more foolish inflation of psychiatry with neurologizing statements which are not made better personfunction by being dressed up in neurological or pseudo-neurological language. On the other hand, a diagnosis of hysteria or neurasthenia or hypochondriasis must no longer be allowed without positive evidence of the disorder and the positive statement and search toward meeting the condition presenting the problem and "mechanism".

Sachs stands firmly on a factual basis.

> "I have considered it my duty in various parts of this address to point out the harm done by *unwarrantable hypothesis*. It is much more difficult to destroy theories after they have once gained a public hearing than to construct them, and instead of advancing our knowledge, they prove to be a distinct obstacle in the path of rational progress."

The address of Sachs warns against such errors or abuses, and it shows his clinical judgment in its concluding remarks:

> "Those of you who have followed my remarks may have concluded that if my arguments are to hold good, the institutions of the care of the insane should be turned over to the charge of the brain anatomist and the experimental physiologist; but I should regret to leave such an impression, for much as I appreciate the help that is to come to the study of psychiatry from the anatomical, physiological, and psychological laboratories, I confidently believe that clinical observation will yield as important results as any of them."

Obviously when I contrast the neurologist and the psychiatrist in Sachs, I keep far from belittling his capacity in psychiatry. Whenever he has had to use his basic conceptions in psychiatry, he has showed excellent sense, but without involving himself with the same attention in the systematic background. He frankly concentrated upon the neurological data in his presentations.

In 1905 when the diagnosis "dementia praecox" was made right and left, obviously to excess and to the harm of both patients and the work, even, or especially, in Kraepelin's clinic,[4] Sachs was the one who started off the discussion in the New York Neurological Association, with his paper in the *Journal of Nervous and Mental Disease*, 32: 353–358, with a sound and reserved, but clear and pointed challenge, and a word of caution. He expressed all the doubts that make us to the present day regretful of the fact that a term doubly misleading should have been pinned to an aggregate of conditions, so varied and so much in need of more specific characterization, if one intends to do more than just put the issue through a statistics machine. Prognostic terminology made Stanley Hall taunt the psychiatrist with the analogy of urging the term "thanatic (deadly) insanity" for "paresis", if "Dementia Praecox" was justified in its own place. It would have satisfied all the needs of the time; but today we have learned that those who called the condition "progressive paralysis of the insane" showed justifiable restraint, implying perhaps that the paresis was something connected with a structural diffuse progressive chronic meningo-encephalitis, most likely pointing to something specifically non-mental, which was indeed finally found to be the spirochaete pallida. And since the spirochaete has proved to be fever-sensitive, the deadly or fatal thanatic property has been shown to be no longer true. Similarly the dementia of dementia praecox, as Sachs puts it, is, on the one hand "never" a complete, or at least radical, dementia, as that of the paretic and senile type, and the disease is by no means always praecox, or sure to come even when favoring predispositions exist. The case is too often complicated by "*diagnosis praecox*", leading one away from the workable facts of the illness and its treatment and understanding.

The second call for caution that resounded in many discussions in Sachs' later years refers to his attitude concerning psychoanalysis. Like many friends and critics of the wave, Sachs objected to the indiscriminate note of exclusive salvation of Freudian doctrine, and its use and abuse, and indeed the very fundamentals of it.

MORE SPECIFICALLY NEUROLOGICAL PROBLEMS

Between 1897 and 1905 there were two interesting contacts, one in the theoretical field of neurology, and one in principles of clinical experience and inferences from the anatomical findings.

The theoretical neurological issue turned on the new orientations in connection with the *Neurone theory*. Two Swiss investigators, the anatomist and embryologist His, and the psychiatrist and biologist and brain anatomist and humanist Forel, had independently brought unity and intelligible order into the chaos of cell and fiber relation representing a divided gray and a white "matter" of the nervous system. His saw the facts from the vantage point of the embry-

[4] Which made the diagnosis in up to fifty per cent of the admissions to the clinic (about as it overdid the diagnosis of General Paresis up to three times the number before Wassermann's tests and cerebrospinal fluid examinations became *de rigueur*. See Kraepelin's remarkably frank and telling frequency tables, 8th edition, 1: 527, and the 9th edition, 1: 759).

ologist: the nervous tissues consisted of cells with a fiber process and specifically nervous functions and glia serving more as structural and vegetative bedding. Forel combined the talent of the patient observer and the experimental way of looking at nerve tissue and the work and methodology of Golgi and that of von Gudden into a conception of the nervous system and perspective rising above that of Meynert; and Waldeyer and others pushed the formulation to the point of speaking of the *neurone theory*. It was a simplification with many valuable emphases and new perspectives, but undoubtedly also open problems, and temptations for generalizations, with understanding and grouping of disease processes and hasty applications in psychology and psychiatry. There were those who began to look for a "psychology and psychiatry of the neurone". And neurology and neuropathology, clinical and anatomical, seemed to divide into camps. The eagerness of enthusiasts made me lose a contest for a prize with a less reserved contestant whose work B. Sachs made one of the points of concern in the Symposium with Barker, Spiller and Donaldson, (*Journal of Nervous and Mental Disease*, 27: 506) my own review having escaped the attention of the discussant.

Sachs sees in it the following points:

It does away with the somewhat arbitrary division of cerebral, spinal and peripheral nervous diseases.

The nervous system is composed of a series of contiguous, not continuous units.

The cell body exercises an important trophic influence on the entire neurone, dendrites, neuraxone and terminal tufts.

Whether contiguity or not the nerve force must in the end pass from one unit to the next.

The laws of Waller and Türck are more easily explained (i.e. have clearer facts to stand on), but one is apt to pile theory upon theory—cell body and nerve fibre are functionally coordinate and equally important parts of the entire nervous system.

There is some advantage in the discussion of toxic effects.

Tabes has been charged with changes of the muscle spindles by Batten, etc.

Piling theory upon theory had better be met by enough knowledge of the facts.

"I cannot sympathize with a recent author (Wolfstein) who believes that the neurone doctrine has reconciled the physical and the metaphysical; it has bridged over the chasm between the material physiologist and the metaphysical physiologist, and joined their hands in harmony."

"The defense of the retraction theory I must leave to one of its chief apostles, who is fortunately in our midst. A substitution of words does not imply an increase in our own concepts. To speak of irritable sensory neurones is just about as vague as to refer to spinal irritability, as we did in former days."

These conclusions are given in full because they show the balanced and judicious evaluation in this field as in the clinical work.

In the meantime Dr. Sachs had, in line with the interest of the family in the educational field, come to gain widening experience in the domain of children's diseases. His attention in that field had early led to the observation of a patient who proved to become a remarkable illustration of the gradual evolution of what constitutes the definition of a disease entity, a specific condition of atrophy of the brain, a particular alteration in the cells of the cerebral cortex; then in the second case of the same family the wider study of the alterations proved to show that the condition was a general one throughout the nervous system, and not only cortical, and constituting a familial disorder really consisting in a very partial disturbance

in the life of the nerve-cell, viz. the accumulation of a product of cell metabolism unable to pass through the cell membrane into the blood-stream.

In the course of time and new observations, the problem has become an interesting one of cell-chemistry and cell-life, and at the same time an hereditary family-limited condition. The development of the history of the problem is similar in a gradual stepwise development of the direction of attention and understanding, common in the history of a wide range of patterns of disease formation and disease types. The gradual understanding of paresis and brain syphilis and of the virus diseases of the nervous system started with limited clues and with advances in what might have looked like very heterogeneous fields of science, a gradual disclosure of processes, some of which of vital importance and leading to special gains in science and in the case of paresis the gain of means of treatment and prevention, and of using in treatment the fever-shy nature of the spirochaete. In the case of the central neuritis, described by me in Brain 1901, there was a similar progression: the finding of the cell alteration (1897), then the passing from Turner's idea of a special mental disease (1899) or an incident of focal brain lesion to the understanding of an incidental disease as central neuritis (1901), and the finding of dependence on a nutritional disorder and the pertinence to the pellagra and food deficit group (Singer), and finally, with discovery of vitamin deficiency, the clue to its control and therapeutic utilization. While the family amaurotic idiocy, or Tay-Sachs disease, is again recognized as a specific problem in the chemical processes in partly race-limited families, it is one of those broadening the perspectives of neurological processes and the constant need of the investigator's becoming proficient in various lines. In this direction Dr. Sachs familiarized himself early with the serological studies in the luetic conditions, and has shown himself particularly open-minded in the management of a fund in support of work in child neurology, the Friedsam Foundation, a reward to Dr. Sachs and a gift to mankind.

PRINCIPLES INCLUDING THE SACHS PRINCIPLE

The ever-recurrent tendency to argue about words for the essence of things has been one of the topics that has almost brought philosophy into disrepute, as a chapter which could be dismissed from present-day education; and actually dismissed from the position of an obligatory part of the training, even at the period of adolescence when general concepts become a natural question; and in the training for our professional schools, such as the natural sciences, history, etc. Whereas a course in philosophy was obligatory and usually in the hands of the College President, the topics are now either left to collateral discussion in the specific problem, or used almost as an expression of opprobrium, as something the scientist, and especially the psychologist, should not mix into his work. All our sciences have to start with certain presuppositions, and their interrelation is naturally of the greatest importance for orderly thinking and work. It is not necessary to repeat all the sins of traditional philosophy, but in view of the fact that traditions perpetuate themselves, there should be a place for the ever-recurrent issues as a history and critique of ideas, and a grammar of method. We shall see that in order to keep the door wide open, it will be found practical to

begin most liberally with the general statement that *anything can be an appropriate item or topic of our general philosophical and scientific concern, the presence or absence and the operation or non-operation of which makes a difference.* This is really just another way of stating *the principle Sachs lays down* in his Morton Prince review—*what is or is not to be discussed.*

It is probably best to see what are the facts of concern, the terms apt to be used, and what those items are in terms of samples. In order to be on safe and practical ground one begins with a concise statement sufficient for *identification*; then where and under what *conditions* found. We must see that one considers the fact first without our disturbing it, together with the setting and the behavior of the item under concern. The next question would be what it *belongs* to, because as a rule, that is the most illuminating help; and only after these two general questions have been done justice to, should one be permitted to see what the item is *made of*, and what it can be analyzed into, the so-called breaking down and the reconstruction. Some of the biggest mistakes in the arguments at hand came from the neglect of these considerations, and from the immediate breaking down of the supposed data to a point far beyond what would still contain the characteristics of the item or object to be discussed, e.g., bringing in molecules where one should use items within the range of the nature of the concern. Pointing to the remarks about the molecules and the question whether or not those are items that belong to the argument, shows up the common error of beginning to speak of matters of pure inference which do not touch any of the essentials of the principle to be looked into. This is the Humpty-Dumpty problem.

This issue, and the results of the previous two questions, the meaning and significance of the items and the pertinence to the problem are finally treated under the *principle of the operative formulation.* The first question is under what conditions does the item occur and operate? Next what are the facts and factors that enter into the operation of the fact or event? What is the mode of operation and the range of results and of modifiability?

This set of principles can readily become an almost automatic line of procedure or of check-up, and it constitutes the very foundation of the relativity and the probability which are essential for non-dogmatic thinking.

One of the most important results of the habitual orientation so outlined is our getting away from merely static verbalisms to the *natural contrasts* between *factual* and *suppositional* and *inferential* or *purely analogical thinking.* It should be clear that the common phrase "the barriers of science are breaking down" may describe the semi-dilettante, or the serious privilege and freedom the human mind has, but calls for respect for the common denominators in a transfer of particles or subdivisions of sets of integers or topics of consistency and clearness of systematization called special sciences or categories, and their special methods and items. The main point has already been indicated, namely, that in the subdivisions of a particular science and field of work, the analysis into parts from a certain point leads us to losing the characteristics of the item we started with. Chemistry divides its items in the direction of chemical pertinence; physics in the directions of quantity, states of matter, solubility, etc., and categories of forces and energetics; and we see that for many sciences it is the belong-

ing together which is the most important, as with the items in astronomy, which we might call macrophysics, in contrast to the relations within the field of living objects, which we call biology, based on structure, and structure and total function.

One is inevitably confronted with the grouping of facts and of sciences according to principles, that one cannot afford to put aside, and one has to arrive at sets of integrates, which form the coefficients or denominators of sets of facts within which one has to recognize wholes and parts, and a general order of procedure, observance of which allows one to outline domains of pertinence as the first thing to be considered in the marking of groups and chapters of study and discussion.

What then about specialization?

We ought to recognize that we assume that fundamental right and obligation in the wealth of experience we have to deal with, to treat *centers of clearness* with the sense of being essential, and to be organized in their own terms and consistent with a sense of reality, but not always in terms which can be carried from one topic to another without a need of caution for the distinctiveness of the denominator of category or integrate. It is as if the language of facts and relationships were basic and essential for each of the special topics of clearness. But we must not allow ourselves to be seduced uncritically to carry what belongs rightfully to one set, into another set, where our habits of speaking and working may readily be of different orientation and bearing. I should speak of integrates or categories, each attending to its own respective business.

I can't discuss mind as a substance, opposed to a body, or split up in three interlocking experiences. Wherever we find mind in action it always has a body. It is organismal, a person. The distinction lies in whether an action uses processes of meaning and significance, with symbolization in planning and memories with what you are occupied with. But that does not cause us to split up the practical unit. As soon as we treat an action such as mentation or a neurological function it has got to belong to something, and that *principle* is a little like what Meynert runs into in singling out his cortex and subcortex. You can logically think of it as if it were "all mind" as far as meaning and intention go, but if it is not *of* the body and *with* the body it would be just abstraction. And I would like to see it in *action* where it gets its effects, immediate and lasting, as we actually see it in life in the whole unit or *person*, the he or she with a biographic character. I never would begin to talk about the "mind" to my students. Nobody would or should want to listen to that. What I want for service is real life and performance, that which has objective validity, but works with subjective self-referring function, with the help of symbolization or thoughts or concepts, or just with our actions where we do a good thing perhaps thinking at the same time of perfectly irrelevant stuff; but definitely where we think and act in harmony or with pertinence to what we consider the issue.

What then about Neurology or Psychiatry? Of course I would say in the first place we are human beings dealing with other human beings on an obligatory basis of reciprocity and fair deal. Within that I am a physician, and that is assuming responsibilities which are reasonably well standardized in our examinations for license. In other words if we are specialists much is required in that particular field; but we have no right to call ourselves specialists if we cannot

furnish evidence of the fact of being humanly intelligent and reasonably informed on what some others might want to be specially recognized for. As psychiatrist I have to think of a wide scope of concrete knowledge, and of the interplay with the surgeon, the pediatrist, the gynecologist and obstetrician, etc. With that as an acceptable basis, I then have to see that I furnish enough concrete data and expression from my own field so as to reach the intelligently shared sense of my non-specialist colleagues and the practitioner and the public whom I want to serve. It thus is essential that we keep in our environment a general attitude and fitness of orientation that is as close as practicable to what we call Hygiene, or in the sense of the Latin equivalent, "vigor" and health, that which maintains itself in progress and process. I would allow everyone to have his status of respect on my part to be what they are, particularly if their self-estimate is substantiated in fact, in harmony with the responsibilities assumed. I respect them for what they are and do, but I consider it my obligation and the optimum of all our concern to realize that there has to be a level of mutual understanding and reciprocity to give us the *freedom and strength* in our respective places.

The Prince review by Sachs is one that undoubtedly also must have had its reverberations in his practical attitude in connection with his work and further pursuit of the problem, or a desire to pass it by. In a way it supplements the Meynert venture of reducing the work with the rich plurality of facts of nature and actuality to what one attributes to but one *part*, the forebrain. It is no doubt a leading part, but inadequate to hold together and explain what common sense leaves or treats as an intelligible group or sub-group, man-function and psychiatry.

It is deplorable that our sense of intellectual morality cannot be trusted and cultivated well enough so that we should not have to separate the thinking of the scientists absolutely and rigidly from his non-professional thinking and action and degree of dependability. Plain sense does not allow me to flirt with the forebrain when I know that I deal with a person with all he belongs to and that belongs to him.

The review of the small book of Morton Prince took us to the field of defining conceptions and relations perhaps not so much of the facts as of the words and concepts which the centuries of written language have passed on to us, while they seem actually to call for description of simple units. The *Nature of Mind and Human Automatism* certainly does hold more for words than for facts that we actually want to meet. It is a great question whether our knowledge of the facts and our interest would bring up the very words and their burden of accumulated meanings, apt to demand disruption of a perfectly natural and simple unit, such as a burst of anger. Dr. Sachs gives a two-page review, which leads him to express *two vitally important principles*, which may well lend themselves to great advantage not only in the particular concern of the book, but as general maxims in our field, namely the demand of being clear on *what is or is not to be discussed*, and to make sure of *our own spontaneous orientation to the question*.

To consider the question in the light of Sachs' principle we should ask first what we mean by "nature of mind." It will be well to consider it first as *word* and the pertinence to a question. The unbiased and critical person would prob-

ably first have to question the worthwhileness of the word "mind" as it is commonly used, since most likely in the connection here implied, one would use a word that designates not so much a substance as an activity or function. This functional character is met by the word "mentation," for the capacity of mental *functioning* which would take us immediately out of the argument about consciousness with a questionable setting and implication and pertinence the whole question. So much of this reminds me of a child's quest—"What is the moon?" or "What does the buffalo do? Does he buff?"

The question about the very essence of things is natural for the child and for the special topic or question, but is apt to deal with the word rather than with the facts.—To begin with the concept and idea of mentation and consciousness, passing by the person, would hardly be the procedure of the Occidental mind. It is the obligation and more and more the habit, to turn to *facts* for which we consider the need of a word. Most of the argument in the present case turns on the *interrelation of terms and concepts*, and the *facts* of experience that have to prove themselves in observation and experiment. The *person* has become the most fascinating topic for the latter part of the last century, and more so today than ever, that which we do best to call *man-science or person-science* as the broad setting in which the physician has to operate and assume his responsibility. With what as the main emphasis in a specialty: The wider frame, or the narrow frame of one of the chief tools?

So much of life consists in the art of keeping within reach of good chance. The finding of and search for illuminating experience, and one's capacity to use and further it, makes up the real rewards and gains of life. There is so much of science "just like life" and of life. Take the Tay-Sachs disease. Few things burst in on us all complete. The stepwise course of events and the need of collateral experience for the making of continuity furnishes the zest of life. First the arrest of development appears as a cortical disease; then a general nerve-cell disease, and a promise that there may be some lack or deficit that prevents the end products of metabolism from finding the way out of the cell and thus cause accumulation,—in its hereditary dependence an equivalent of the pyruvic acid problem. All of this means open mind and patience and preparedness for further assimilation.

Meynert's urge has not lost its vigor in the life-time of Sachs, but it has broadened its field. There is no longer the expectation that focussing on a pet preoccupation should bring the solution of the widely pluralistic and pragmatic issue of man's health and vigor. Prince's preoccupation with an egocentric panpsychism did its work and influenced the rest of his work. Sachs' trend was towards letting the nervous system tell us more and more, and furnish us opportunities where they could be found and used; but he also kept the broad sense for the person open and sympathetic, unless it became too onesided and over-assertive.

We are in a stage of multiple readjustment. There has to be a place for frank recognition of the leading function of man, not but one leader and the rest machine: with a respect for specialization, not in the sense of isolation, but rather emphases in sound settings, and reciprocity and fair deal. *Bringing the person into science and medicine, and making it intelligible and productive has been the main goal of the broad, and yet intensive, psychobiology.*

Psychopathology learned from the crude experiments of tissue pathology and vascularity and the data established by the clinical experiments of the organicists; focal and general, in tissue diseases, and in the infections, and in the metabolism disorders. But psychopathology, or person pathology, truly pluralism fashion, found itself in expansion within its field of experience and processes.

The most world-wide spectacular stroke of genius and fate was that of Freud and Adler and Jung—perhaps too much and often turned into clichés and patterns or mechanisms. It arrived at a time when psychology at large still refused to be dynamic, and remained orthodox and too formal, whereas the Freudian movement appeared in the garb of absolute determinism, vigorous but revengeful, built on conflicts rather than a general conception of life.

On the one hand "behavior" became dominant, with Mercier as conduct, and under McDougall and Watson behavior. Then there came the interest in action generally, and not only in sensation: the interest in a psychobiology of the unit or person, the undivided whole in *ergasia*.

In this country the broader non-exclusive, but not merely eclectic movement was that of psychobiology, not specific and glamorous enough to bid for the "front page," with its change toward objectivity, on the one hand the courage to see things as found, and on the other, the refusal to be impressed by words and vocabulary of largely tradition-born thought and in contrast to the rise of both practice and public response in the release theory of sex, and the escape phraseology, and the gift of courtesy called sublimation.

There was also the Prince trend toward keeping the flame of hypnosis active and in well-planned use and utilization.

In all of these releases and liberations and direct interest in sound opportunity Sachs had a frequently moderating, but also activating, influence: a genuine example of the promotor of sane principles, which he himself sketched in these maxims:

1. Broad preparedness in the natural sciences, as well as the cultural ones (Charaka Club).
2. A determination to succeed.
3. Hard work, availing oneself of every opportunity.
4. Devotion to the patient who is not a mere case.

I wish that when this reaches him, Dr. Sachs might favor us with his own vision of reminiscences, and help us add the human element so important in the shaping of actuality—so sadly jolted today by whole nations not being willing and able to respect one another with the right to be different, but sure of the right to be respected and willing to collaborate in council and responsibility, some times as leader and again in the ranks, democracy-fashion.

EVALUATION OF DR. SACHS' CONTRIBUTION

What is it Bernard Sachs has achieved? There are discoverers and inventors and creators and performers and examples and teachers, persons who make the wheels turn faster or more smoothly and favorably and in whose hands and ways of functioning others find help and sense. There are those whose very existence is a great occasion as much as cause of benefit and comfort and reorganizing of soundness. In stability of progress rather than in startling departures and novel

events and inventions, he was and is a real and specific influence, and the type of whom one feels and wishes that there might be more of them—in action and council and in production of balance and coordination. One would like to find and spread and cultivate the secret thereof—if we need speak of secret? We might well wish for the best possible knowledge and accessibility of what constitutes that happy, fortunate and opportune quality, a factor of progress rather than what we call revolution, perhaps closer to the truer non-catastrophic meaning of revolution, a help and creator of orderly development and growth, non-explosive, pacific, and allowing pacts and peace to shape and last, free of artificiality or of luck at the expense of others. He is the occasion of a harmonious and consistent word picture, each portion of which would be a real contribution. There are not many, not enough of the kind, more widely evaluated and appreciated.

Bernard Sachs was at his best in the role of the re-establisher of balance in the relation between neurology and psychiatry, operative largely in neurology, but by no means exclusively so, a physician not merely of physic, a highly respected colleague and doer of much good with a life well-lived—non-spectacular, but highly appreciated, effective exemplary. A center of soundness in followership as well as coordination.

The item with and through which his name has its lasting status is characteristic of a mark in neurology. It is a find rather than a creation. The Tay-Sachs disease is a real challenge, not frequent enough to be a startling item, but one which, like the pyruvic acid discovery, represents a hereditary peculiarity producing a retention disorder in contrast to a deficit disorder, like the one that formed a kind of duplicate in my central neuritis type of disorder, also described as histologically specific before the specific principle was established.

The writer of these notes senses many parallels and equivalents or analogies in what made him a psychiatrist whereas Bernard Sachs became a neurologist.

One would like to get at the objective data giving the natural background for some of the developments and specificities in this interesting and intelligible and enviable life-record: a development in a teacher's family, in a period of great gains in neurology, and neurologically more contributive than psychiatrically. What within neurology? What within psychiatry? The neurological field giving special renown in leadership.

Our own life-time has brought us a new and more workable concept and practice of pathology, including the whole of man and man's relations. Medicine has been enriched by the inclusion of the person, and the new sense of medicine has enriched prophylaxis and hygiene, the science of *vigor*.

Bernard Sachs is one of those who have fully earned the fruits of a healthy and exemplary service in an age and field in which he is honored as the highly respected colleague and friend, unfailingly true to the ideals of a remarkable period. He was known how to focus his energy and wisdom on the experiences of several generations, and at the same time spread his influence over a wide range of sound practice. A conservative progressive, a sound practitioner, a man of well-balanced judgment and a fair distributor of helpfulness. May he long enjoy the fruits of his labor and the rewards for what he is to his world and to the wider world.

BERNARD SACHS

The Founder of the International Neurological Congresses

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[*New York*]

The plans for the First International Neurological Congress which was scheduled to be held in Paris in 1914 dissolved in the carnage of World War I and a similar fate descended upon the proposed Fourth International Neurological Congress which was planned to be held in Paris in the Summer of 1943. In the intervening years, however, much of constructive value was written into the history of neuropsychiatry and the major credit for this accomplishment should be given to the Dean of American Neurologists, Dr. Bernard Sachs.

It was inevitable that a considerable number of years had to elapse, before the bitter memories of World War I could become dulled sufficiently to allow the minds of neurologists the world over, to return to the idea of an international neurological congress. The first attempt at international collaboration along neuropsychiatric lines originated in the plan for a combined meeting of the American Neurological Association and the Neurological Section of the British Royal Society of Medicine. In the United States, Drs. Sachs, Weisenburg and Tilney were actively interested in the project as were Drs. Holmes, Purves-Stewart and Wilson in England. After much consultation and planning, a most successful meeting was held in London in the summer of 1927 and all of the Americans who attended the gathering returned to this country enthusiastic over the success of this meeting and inspired to further such occasions on a larger scale.

In the Summer of 1928, by a fortunate chance, Otto Marburg of Vienna and Bernard Sachs of New York met in Bad Gastein. Their mutual interests led to repeated contacts and developed into a firm friendship. In the course of their many conversations, their thoughts frequently turned to the idea foremost in their minds, namely, the development of neurology and psychiatry throughout the world. It was the belief of these two scientists and physicians that Neurology had not yet reached adult stature, nor had it received the recognition in the Universities, particularly of the continent, which it had gained in the eyes of the public due to the emphasis and publicity which had fallen upon it in the World War I and the years which had followed that catastrophe. Separate departments for Neurology had been established in many American universities, but in numerous other localities, Neurology was still looked upon as a branch of Medicine. It seemed to Drs. Sachs and Marburg that an International Neurological Congress would serve to focus attention on the coming-of-age of Neurology and that the prestige of the specialty would be greatly enhanced by such a meeting. They believed that the national neurological organizations of a large, number of countries could be interested in such a project and, as it turned out their faith was well founded and rewarded.

The countries of Europe, still driven by post-war jealousies and antagonisms, were in no position to organize such an attempt at international collaboration

and Dr. Marburg felt that the only group which could initiate such a movement and carry it to a successful conclusion was composed of the neurologists of the United States of America. After many conversations, it was decided that Dr. Sachs should prepare such a proposal and submit it to the American Neurological Association for discussion. As soon as this decision was reached Dr. Sachs consulted with representative friends living in France, Great Britain and Germany and received from them enthusiastic responses and promises to present a proposal for an International Neurological Congress before their national organizations.

Upon returning home in the Autumn of 1928, Dr. Sachs discussed his plan with a number of the more active members of the American Neurological Association and encouraged by the response which was evoked, a concrete proposal was drawn up and submitted to the Council of the Association. The suggestion met with immediate enthusiastic interest, for many of those present had attended the British-American meeting in London in the Summer of 1927 and were filled with the delightful memories of that eventful and profitable meeting of British-American confreres. A committee was appointed by the Council and it was natural that Dr. Sachs be elected Chairman with the other members consisting of Drs. Cushing, Dana, Meyer, Tilney, Weisenburg and Dr. Riley as the secretary of the Committee. It was decided almost without argument that Switzerland was the natural place for a neurological congress as it had not been a belligerent in the World War. Another and equally compelling reason for this choice was the fact that Berne had been previously chosen as the meeting place for the International Neurological Congress planned for 1914 but abandoned because of the outbreak of the First World War.

There then ensued correspondence with the Swiss neurologists in order to determine whether these plans would be acceptable to them and their immediate acceptance added momentum to the project. Dr. Bing of Basel was particularly enthusiastic and was of great assistance. The Swiss neurologists, appreciative of the honor of the choice of their home-land for the first congress, were unanimous in their approval and unremitting in their efforts to make the project a success.

In the late Autumn of 1928, it was decided to call a preliminary meeting of delegates from as many national organizations as could be interested, for the purpose of organizing the future congress. The chief burden of the organization of this preliminary meeting fell on Dr. Sachs' shoulders. His wide personal acquaintance with the neurologists of many nations opened the door to informal correspondence with them and almost without exception promises of active support and collaboration were forthcoming. It is a great tribute to his universal popularity that these promises did not die with the breath which uttered them but blossomed into the active cooperation which made possible the organization of the Congress.

The New York committee attempted and in great part was successful in establishing contact with the neurological societies of countries scattered from Canada to Chile, Norway to South Africa and those in the Far East, Japan,

China, Australia and New Zealand. Almost without exception the response was enthusiastic and the active support of twenty national societies was obtained in the organization of the preliminary program-executive committee meeting which was held on August 29 and August 30 at Berne and was attended by about thirty delegates. Previous to this meeting, Dr. Charles Dubois of Berne had been chosen to act as the secretary of the Swiss Committee and this choice was a most happy one; much of the success of the preliminary meeting and of the congress was due to his diplomacy, efficiency and particularly to his knowledge of European conditions and personalities.

The meeting was presided over by Dr. Sachs, the chairman of the committee for the American Neurological Association, and as was most fitting and appropriate, he was unanimously chosen by the delegates to be the President of the First International Neurological Congress to be held in Berne, August 31 to September 4, 1931. This preliminary meeting was a most successful one, dinners and luncheons were given for the delegates, their wives and children, and the presiding officer, Dr. Sachs, contributed a gracious and tactful influence to the social and professional gatherings. At times, delicate diplomacy was necessary and the fact that nothing ruffled the smooth surface of the meeting spoke volumes for the kindly, considerate and skillful hand, heart and mind which made possible a safe course through many hidden whirlpools and potential rapids. The meeting adjourned after two days devoted to the choice of topics for symposia, the arrangements for individual presentations, the types of membership, the ways and means for the support of the Congress and the plans for the entertainment of the delegates and the members of their families.

In two years which intervened between the organization meeting in 1929 and the congress in 1931, the President and the Secretary-General were busy almost continuously writing letters to enlist the collaboration of as many national organizations or individuals as could be reached. Where there were no national societies, individuals were sought out and in suggesting these personal contacts, great assistance was provided by the other members of the Program-Executive Committee who by reason of their international acquaintances were able to suggest those who would be most influential and best able to arouse interest in the Congress.

The appointment of a local committee and of Dr. Dubois as local secretary relieved the President and the Secretary-General of much of the detail in connection with the local arrangements, the entertainment and the housing of the delegates and their families. During the Winter of 1930–31 the task of organizing the scientific program was the chief issue and here Dr. Sachs' long experience in program-making for many societies and associations was of inestimable value. It was remarkable and a great tribute to the tact and diplomacy of the President that only one crisis threatened the smooth progress of the committee. This difficulty arose over the premise that the Program-Executive committee would act as a real program committee and select the papers which would be presented at the sessions for miscellaneous papers. After enormous labor the lists of titles were sent to all of the members of the Program-Executive Commit-

tee, votes were taken and tabulated. But when the final choice of those who would be admitted to the programs of the smaller sessions was about to be made, one of the delegations threatened to withdraw the support of its entire national group, and it was one of the largest, if the program were to be organized on a selective basis. This delegation believed that a place on the program should be made for any member who wished to present a paper irrespective of its merits. A rigid insistence upon the decision of the Program-Executive Committee to carry out a real selection of papers to be presented was urged; but fortunately, this course was discarded by the greater wisdom and experience of Dr. Sachs, the terms of the insurgent committee were accepted and the preparation for the Congress sailed on over unruffled waters.

The Congress opened auspiciously with the large hall of the Casino at Berne filled to overflowing with members and guests. After several addresses of welcome by the Swiss national officials, the opening speech by the President, Dr. Sachs, was received with great applause and set the entire tone of the meeting on a high level. Dr. Sachs thanked the Swiss officials for their cordial reception and sympathetic greetings. Excerpts from his speech may well illustrate the spirit with which the Congress opened:

"We neurologists are happy to meet in the very heart of this glorious Swiss country, to enjoy its soul-stirring scenery, its marvellous lakes and mountains, its fine cities; to learn to know its sturdy people, and to be inspired by the memories of those early days, over six centuries ago, when Swiss heroes made the first successful stand for human liberty.

"It must be a great satisfaction to the government and to the people to realize that they are extending their hospitality in this period of world stress to a fraternity of medical men in forty-two different countries, who, irrespective of national boundaries, and often at a great personal-sacrifice, have come from every corner of the globe to further the special science to which they are devoted and incidentally to promote international friendship and the well-being of their fellowmen in every land. . . .

"The purpose of this congress is primarily to establish personal contact and to unite the neurologists of the entire world in the attempt to find a solution to the many important problems engaging their attention; to indicate other problems that will call for study in the immediate future, and to emphasize the important relation that neurology bears to every branch of medical and surgical science. Neurology is the fundamental specialty of medical art. Without a thorough appreciation of its truths, medical and surgical science is like a ship floundering about in a turbulent sea without helm or rudder. . . .

"A thorough knowledge of neurology should play an important part in every medical curriculum; and in every hospital nervous disorders should be treated in special wards and by men and women especially trained and fitted for such work. We neurologists have suffered from an excess of modesty, or a minimum of assertiveness; while others have cried from the housetops. The proceedings of this congress will, I am certain, give ample evidence of the importance of neurology in the medical and surgical sciences. But let me add that we recog-

nize a definite reciprocal relation with medicine, with surgery and with psychiatry. Mental and nervous diseases cannot be studied apart. In neuroses and psychoneuroses, established neurologic data furnish the reliable background and the criteria by which all new theories, however fanciful, are to stand or fall. With neurosurgery we are so intimately and permanently allied that divorce is unthinkable. The neurosurgeon must be steeped in neurology, and the neurologist must follow with keenest interest the work done by the neurosurgeon. Our problem proves that the neurosurgeons and the pure neurologists, if any of us are pure, have identical problems.

"I invite you now to the consideration of some of these problems."

Dr. Sachs proved to be an ideal presiding officer and the sessions of the Congress were full of interest and proceeded smoothly to their termination. Luncheons and dinners given by the President contributed greatly to the success of the meeting and were thoroughly enjoyed by those who were invited to these entertainments. One of the most successful of the social events of the Congress was a "smoker" held on the evening of September 4, the concluding day of the Congress. This gathering was made possible through the personal generosity of Dr. Sachs who, with his customary modesty, insisted that ostensibly the event was given at the invitation of the American Neurological Association. It was attended by a large gathering of the members and guests and served as an appropriate and fitting close for the First International Neurological Congress, whose success was so greatly due to the guidance and personality of Dr. Sachs

No description of the relation of Dr. Sachs to the series of congresses could be complete without a word of appreciation for the splendid achievements of all of the members of the local Swiss committee who developed the local organization and prepared and carried into effect the multitudinous details concerned with the large and small meetings, the housing of the delegates and their families and the social events which graced the Congress. Space does not permit nor would it be appropriate here to speak further of the enthusiasm displayed by all of the organizers of the Congress, except to point out that all of this spirit was engendered, fostered and developed by the guiding hand of the President.

The executive session of the Congress decided that the Second Congress would be held in London in 1935. Dr. Sachs continued as the active President until the Program-Executive meeting of the delegates was held in London on September 6 and 7, 1933, at which time Dr. Gordon Holmes was elected President of the Second Congress. The six months preceding this meeting were devoted to the routine correspondence and arrangements with the local London Committee and the representatives of the various constituent national groups which made up the First Congress. At the Program-Executive Committee Meeting Dr. Sachs was elected the First Honorary President of the Second International Congress, which was held in London from July 29 to August 2. Relieved of routine duties, Dr. Sachs' responsibilities were less arduous and he was able to devote himself to contacts with the members of the Congress and their families in informal and intimate social engagements.

The Executive Session decided that the Third Congress would be held in

Copenhagen in 1939 and the organization meeting in the same city in 1937. During these years Dr. Sachs devoted himself to the maintenance of the enthusiasm of the members of the Congress both in the United States and foreign countries for the series of Congresses. The American Committee had no formal responsibility for the Third Congress but Dr. Sachs continued as the First Honorary President, having associated with him as the Second Honorary President Sir Charles S. Sherrington and Gordon Holmes as Third Honorary President. Unfortunately, serious illness in his family prevented Dr. Sachs from attending the organization meeting on June 29 and 30, 1937 and the Congress from August 20 to 25, 1939 in Copenhagen. His interest was, however, undiminished and frequent meetings during the Winter of 1938–1939 were held by the New York members of the American Committee for the purpose of arousing interest, stimulating members of the Congress to contribute papers and encouraging the attendance of Americans at the Congress. The Third Congress, held under the imminent threat of a general European war, was successfully carried out. The relatively large number of American contributions and members was largely due to Dr. Sachs' unremitting interest and activity in forwarding the purposes of the Congress. The Congress was disturbed by a general feeling of apprehension and distrust and was flooded with all sorts of rumors of warlike activities. Naturally, the Polish, English and Dutch members were particularly affected by these conditions and many of them returned to their homes before the conclusion of the Congress. Those who remained carried on to the best of their ability and the audiences continued to be interested and appreciative of the efforts of the officers of the Congress and the Danish hosts who did everything possible to allay the general feelings of apprehension and fear. Fortunately, the Congress was able to complete its activities before the actual opening of hostilities. The invasion of Poland began early in September and seriously interfered with the return of some of the members of the Congress to their homelands, but so far as is known no casualties were reported. Some of the American members were marooned in Norway and other ports for upward of a month, during which time their foreign confreres did everything in their power to make their enforced stay of benefit, socially and professionally.

It is of interest that the members from the aggressor countries remained until the very end, although some of them at least must have been acquainted with the plans of their war lords and diplomats. No whisper ever was heard, however, and the German representatives were active in the plans for the Fourth International Neurological Congress and in the choice of Paris for the meeting to be held in 1943. It is to be presumed that they believed that such a Congress would be held under the beneficent and cultured overlordship of the Nazi ideology in its new French dependency.

The series of three Congresses can be looked upon as being preëminently successful in stimulating Neurology to assume its full importance in various countries where as yet it had not reached full fruition of its potentialities. Resolutions passed by various Executive Sessions played a definite part in the growing appreciation of the importance of neurological and neuropsychiatric matters.

Although many contacts have been blasted by the unhappy fate of the world in September of 1939, other contacts with countries capable of more humanizing and cultural activities have resulted in a greater internationalism, appreciation of common problems and perhaps of more importance than anything else, friendships which shall endure. These benefits are the result of the foresight of Drs. Sachs and Marburg in the years preceding the first organization meeting in 1929. To no one is due greater appreciation than to Dr. Sachs for his far-sighted vision and development of the idea of the series of International Neurological Congresses. His contribution toward the establishment of social, cultural and professional contacts between neuropsychiatrists of all nations is an enduring one and too much gratitude cannot be expressed to him for his ability to organize such occasions and his never-failing tact, diplomacy and genuine human friendliness in making these events the great successes which they have been.

Although temporarily interrupted by a world-wide madness, it is certain that the movement initiated by Dr. Sachs will continue and that as soon as circumstances permit, the series of Congresses will be resumed. It is to be hoped that this resumption of the discussion of communal interests may emerge in a saner, wiser and more self-understanding world, and that the American Neurologist who will again serve as the leader in this field of scientific endeavor will be Dr. Bernard Sachs.

INTIMATE REMINISCENCES

ALFRED WIENER, M.D.

[*Consulting Ophthalmologist, St. Luke's Hospital, New York*]

Chatting with an old locomotive engineer, he told me that his first month at the throttle of a steam engine drawing a passenger train, had been to him a period of almost continuous anguish. The thought of all the human lives entrusted to his care proved a burden almost more than he could bear.

The conscientious young physician is in a similar position, and suffers, often, from the same sense of crushing responsibility. He needs beyond all else the assurance that comes from experience and from the generous support of his seniors in the profession. To a very great number of young medical men still in this stage of acute sensitiveness, Bernard Sachs was an unfailing source of inspiration and encouragement. He liked his juniors, helped them whenever and wherever he could, stimulated them by his personal open-mindedness to develop their powers, and to form and express their own independent conclusions. Many a physician of rank today, owes his start in his early efforts in large measure to the helpful cooperation of Dr. Sachs.

My own early experience is a case in point. In the early nineties of the last century, some fifty years ago, Dr. Sachs served as Professor of Nervous Diseases at the New York Polyclinic Hospital, then located on East Thirty-fourth Street. I had completed my medical studies in Europe, after graduating from the College of Physicians and Surgeons, and had become Adjunct Professor of Nervous Diseases under Dr. Sachs. He lectured three times a week, in addition to the notable service he performed in the clinic. His lectures drew large classes of post-graduate students; usually at least fifty to seventy-five men attended. Dr. Sachs was an admirable talker, with a true sense of logic, and an unfailing ability to clarify the most abstruse subjects. His vividness of illustration and humorous approach made his lectures fascinatingly interesting and universally popular.

Therewith a real diversity in viewpoint derived from his constant willingness to accept suggestions from his assistants, and incorporate them in his talks. Many contributions were made in this way by two younger men, destined later to achieve great reputations, Joseph Collins and Frederick Peterson.

My own chances to contribute to these lectures, which Dr. Sachs always prepared with the greatest pains, were frequent. Two instances that I still recall, were typical. Dr. Sachs had in mind the delivery of a lecture on the subject of brain lesions. After we had discussed various forms the lecture might take, I suggested the employment, as a demonstration, of a living monkey with its brain suitably exposed; and its motor centers stimulated through the application of a faradic current. Such an experiment was then altogether unusual, and might well have been rejected as too risky from several angles, by a man less open-minded than Bernard Sachs. He, however, consented at once to trying it.

Such a monkey was then procured. The parietal portion of the skull was

removed, and the motor area exposed, leaving the dura intact. The monkey was anesthetized each time and with an electrode attached to the faradic battery, the face, arm and leg centers were easily stimulated, and produced action by contractions of the respective members governed by these centers. Strict cleanliness, antiseptic precautions with a suitable metal cap, kept this monkey alive for about two months. He lived with our janitor in the basement of our institution, where it was warm especially amongst the steam pipes, and from which each time I had to entice him with his most acceptable food, viz., bananas. This whole procedure was a most convincing demonstration and highly satisfactory to the student.

In another instance, the subject of a proposed lecture was to be Hysteria. My idea in this case was to employ hypnotism, a technique I had studied intensively abroad, to achieve the innovation of demonstrating an actual hysterical convulsion before a class of students. This would have been, at that time, a daring innovation, and acceptance of the idea called for great courage on the part of a lecturer of established reputation. Dr. Sachs consented at once to my making the effort.

We had, then, in our clinic an hysterical patient who suffered from such attacks. My task would be to use hypnotism to bring on an attack, instead of the more customary procedure of using it to avert one.

We first attempted the experiment outside the classroom, and with complete success. Thereafter we repeated the demonstration before the class, producing a veritable sensation.

Dr. Sachs was then a pioneer in the study of Nervous Diseases, in which he had specialized. He had concentrated on Nervous Diseases of Degeneracy, as well as on Nervous Diseases of Children. One particular disease, Amaurotic Family Idiocy, to which he had given profound study, is still known to most physicians by his name.

Many papers and published articles of notable value made his name familiar to all his colleagues at that early period. Later his reputation was further enhanced by the publication of his book on Nervous Diseases of Children, later rewritten in collaboration with Dr Hausman: "Nervous and Mental Disorders from Birth Through Adolescence."

My own interest, of many years standing, in Nervous Diseases, I attribute principally to my association with Dr. Sachs. It led me even to experiments pointing to my own future field in diseases of the Eye, Ear, Nose and Throat. One early experiment in that direction, encouraged by Dr. Sachs, which I still recall, was the case of a teacher who had lost her voice a year before, which we were able to restore to her through hypnotism combined with orthodox local treatment. This constant interest in Nervous Diseases has been of continuing use to me in my own field. It has proved of frequent utility in the location of brain lesions through the eye; and has also helped frequently in connection with ear diseases. I am strongly of the opinion that every oculist would be the better for some knowledge of nervous diseases. In the light of that feeling, I find myself increasingly grateful to Bernard Sachs for the help I derived from his teaching in my formative years.

DR. BERNARD (BARNEY) SACHS—BIOGRAPHIC MILESTONES

LOUIS HAUSMAN, M.D.

In the preparation of Dr. Sachs' biographic milestones and bibliography, I have been struck by two things: one, the vigor of a long scientific life which can be measured even more fully by its deeds than its years; the other, the comprehensive attitude of a searching mind, interested in the feelings and heart throbs of the patient, as well as the facts and figures of his disease.

It is worth noting that the title of the first article, presented in 1878 as a Harvard Commencement Oration, is: "Goethe As A Man Of Science." Even at that early date, when Barney Sachs, despite his A.B. degree with honors in Natural History, was only twenty, the interest was in Goethe the man and Goethe the scientist; in "Goethe the poet, whose works teem with wonder and admiration for nature's laws, and Goethe, the man of science, who finds in them the realization of sublime principles." The search for truth had already begun.

In this quest of 1878, the young man Sachs is already attracted to the discovery, by the author of Werther and Egmont, that the skull is in a certain sense a repetition of the spinal column. This interest in "the hidden treasures of anatomy" presages the great medical discovery of the young doctor in 1887. It may seem longer, but the span is only nine years, from the time the Harvard student showed an academic interest in the vertebral theory of the skull, to the year of his medical studies in arrested cerebral development and the recognition of Amaurotic Family Idiocy as an entity.

It is given to few men to make their mark, with such distinction, at twenty-nine. The corollary of such success is optimism. In this respect Dr. Sachs was no exception, although I suspect that he was cheerful and hopeful, even before his career turned his disposition into a point of view. He had every reason to find the application of the Socratic injunction—know thyself—a most pleasant one. But personal experience, alone, does not beget optimism. Reason, intuitive reason in the sense of Pascal, is a necessary attribute. I believe that Sachs, like Leibnitz, who gave the doctrine of optimism its name, is of the opinion that everything in nature is ordered for the best. Perhaps he would add that one special principle of nature—hard work—is essential to produce the highest good.

That ripened experience has not changed this outlook, nor the years narrowed its range, is evident if we scan the bibliography once more. At the bottom of the list opposite the year 1942, i.e., sixty years after he received his medical degree, is Dr. Sachs' recent article: "Be An Optimist." A philosophic attitude is now a therapeutic principle. Dr. Sachs, still interested in the individual, writes of the heart and counsels the cardiologist and the general practitioner to "be humane, be cheerful and hopeful."

In the appended bibliography are recorded the deeds of a pioneer in neurology. It is well to remember that the Babinski reflex and the Wassermann reaction were still unknown, when Dr. Sachs was reporting the following: "Ueber Den

Einfluss Des Rueckenmarks Auf Die Harnsecretion" in 1881; "on the use of the galvanometer" in 1882; on "tumors of the spinal cord" and on "arrested cerebral development with special reference to its cortical pathology" in 1886; and, in subsequent years, on the infantile cerebral palsies and the surgical treatment of epilepsy and of trigeminal neuralgia. Because of these researches and their contribution to the wisdom of the future which they helped to shape, the time of this neurological chronicle is endless and its years unnumbered.

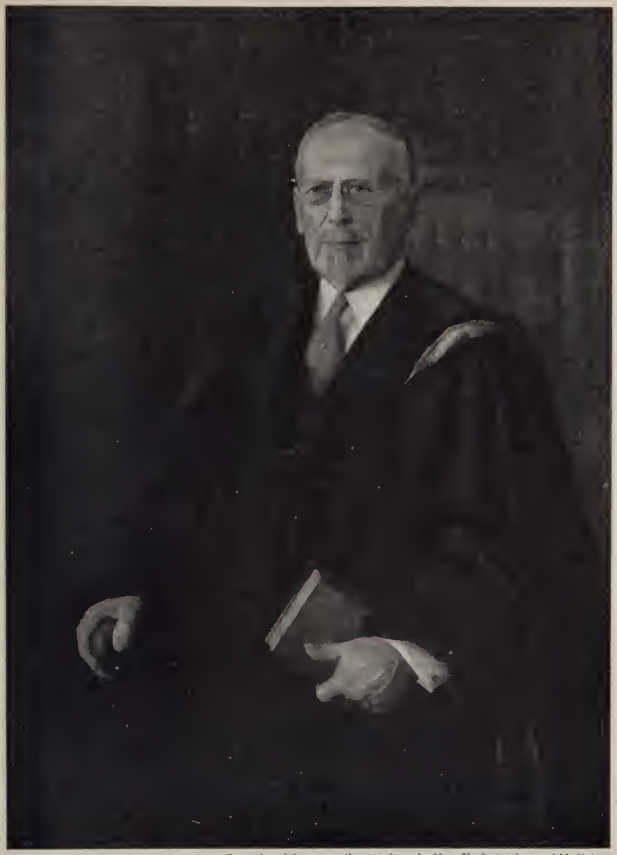
The flow of production which began in 1881 has helped to cultivate many fields in neurology. The stream of thought has been fresh and clear; the current strong—strong enough to clear away the underbrush and cut new paths. Obstacles have served only to emphasize the strength of the current, as it either swept them aside or carried them along in the wake of its course.

The biographic milestones along the banks mark well the progress of the stream. Those of us who have been so fortunate as to sit by the banks, have found the stream deep; the view broad and the waters not without sparkle. We have learned to understand and appreciate:

"The glory of action
The bliss of growth
The splendor of beauty."

DATES AND EVENTS IN THE SCIENTIFIC CAREER OF DR. BARNEY (BERNARD) SACHS

Entered Harvard College	1874
Received A.B. degree with honors in Natural History	1878
Studied medicine in Strasbourg, Alsace and Berlin, received M.D. degree	1882
Postgraduate student with Meynert at Vienna, with Hughlings Jackson at London and with Charcot at Paris	1882–1884
Returned to New York	1884
Instructor, New York Polyclinic Hospital	1885
Member of the American Neurological Association	1886
Neurologist, Montefiore Hospital	1887
Professor, New York Polyclinic Hospital	1888
Consulting Neurologist, The Mount Sinai Hospital	1893
President of the American Neurological Association	1894
President, New York Neurological Society	1896
Honorary Member Moscow Neurological Society	1898
Alienist and Neurologist to Bellevue Hospital	1899
Chief, Neurological Service, The Mount Sinai Hospital	1900
President, New York Neurological Society (second time)	1908
Consulting Neurologist, The Mount Sinai Hospital	1924
President, First International Neurological Congress, Berne	1931
President of American Neurological Association (second time)	1932
Professor, Clinical Neurology, College of Physicians & Surgeons, Columbia University	1933
President, New York Academy of Medicine	1933–1934
Director, Division of Child Neurology, Neurological Institute	1934
Corresponding Member, Royal Society of Medicine, London	1934
Director, Child Neurology Research (Friedsam Foundation)	1936
Senior Consultant, Division of Neuropsychiatry, Montefiore Hospital	1942



Reproduced from an oil portrait at the New York Academy of Medicine.

BERNARD SACHS, A.B., M.D.

President of the New York Academy of Medicine, 1933–1934

DR. BERNARD SACHS—HIS CONTRIBUTIONS TO THE SCIENCE AND ART OF MEDICINE AND RELATED TOPICS

1877. Harvard. Bowdoin Prize Dissertation. A Comparison of the Fore and Hind Limbs of Vertebrates.

1878. Harvard Commencement Oration: Goethe as a Man of Science.

1881. Ueber den Einfluss des Rückenmarks auf die Harnsecretion. *Pflügers Arch. f. d. gesamte Physiologie*, 25: 299–322.

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1885. Book Review: Die Elektricität in der Medicin. Von Dr. Hugo V. Ziemssen. *Journal of Nervous and Mental Disease*, 12: 491.

1885. Translation of textbook: Psychiatry. By Theodor Meynert, New York and London, G. P. Putnam's Sons. (Translated under authority of the author by Dr. B. Sachs.)

1885. On the Use of the Absolute Galvanometer with Description of Hirschmann's New Instrument. *Journal of Nervous and Mental Disease*, 12: 19–26.

1886. Book Review: Die Thomsen'sche Krankheit (myotonia Congenita) Studien. By Prof. Erb of Heidelberg. Leipzig, F. C. W. Vogel.

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1890. Cerebral Hemorrhage, Thrombosis and Embolism. Keating's *Cyclopedia of Diseases of Children*, 4: 525.
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1891. Multiple Cerebrospinal Syphilis. *New York Medical Journal*, 54: 309–314.
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1892. Morvan's Disease. B. Sachs and S. T. Armstrong. *New York Medical Journal*, 55: 482–486.
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1898. A Review of Dr. Seguin's Contributions to Medicine. *Medical News*, 72: 582–586.

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1909. The Common and Uncommon Localization of Otitic Brain Abscess as Illustrated by Two Cases with Recovery. B. Sachs and A. A. Berg. *Medical Record*, 75: 129–133.

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1910. Raymond de Vieussens, Noted Neuroanatomist and Physician of the Seventeenth Century. *Proceedings of the Charaka Club*, 3: 99.

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Commencement Part

by

Barney Sachs '78

Subject "Goethe as a man of science."

Goethe as a Man of Science.

'The world has long since recognized very soon that as a poet,' said Goethe, 'but few are willing to consider that I have studied Nature carefully and on all its phases.' The poet's complaint has lost some of its force in the half century that has elapsed since his death: Many however are still ready to ascribe to him the enthusiasm of a novice and to ridicule the mere dabbler in science. Why then, place Goethe in the foremost rank among men of science?

His claims rest upon a long and thorough study of Nature, upon the profession and exercise of a true scientific method, and, not least, upon three important discoveries in Botany & Zoology which gave a new impetus to the study of these sciences. While his fame depends upon his work in the organic sciences, his theory of colors reveals the earnest student of

the purely physical sciences. The poet of Weimar was proudest of his physical researches, and yet in these he signally failed. His simple and acute reasoning concerning the phenomena of Nature could not overthrow the strong experimental proof of the Newtonian theory. Goethe's comparative failure in physics heightens by contrast the merit of his work in other sciences.

His wonderful success in solving the problems of organization was not the result of grand poetical inspiration. It must be ascribed rather to the continuous development of his own mind and to the thorough scientific training he enjoyed from his earliest years. The poet cares but for truth and seeks it steadily until he gains admittance to the Temple where the book of Nature becomes more legible to him. His keen understanding of nature's laws was first made manifest in his discovery of the intermaxillary bone in man. It was not the bone itself, but the introduction of the new and

revolutionizing method which led to this discovery (that is, geologic reasoning). This bone was said to be entirely wanting in man and was constantly employed as an argument to deny his intimate relation with the animal world. On the other hand, Goethe argued, that the presence of this bone in the higher animals implies its presence in man. And his research verified his logic. In other words, he distinctly declares the uniformity and persistency of nature - an idea which in his day appeared paradoxical to many. At present the phrase unity of nature has become familiar to all, but to appreciate fully the great value of the introduction of this principle and of the comparative method, the man of science and the enthusiast to-day must give themselves a reckoning nearly a century ago when the details of nature alone received attention, when every species was considered an isolated creation entirely independent of all else.

Whatever phase of Nature Goethe was studying his was constant

by guided by this principle of unity. All his theories, in fact are but special elaborations of this one idea reached by the universal application of the comparative method. Thus was he led to that beautiful doctrine of the metamorphosis of plants - a doctrine which gives additional strength to the science of morphology. The ordinary observer sees in the various parts of plants and animals certain organs subserving certain ends or functions. The morphologist sees in that same part not functional perfection, but a member of a community, modified, perhaps, from some original form. And so Goethe has taught us to look upon the flower not merely as an aggregate of calyx, corolla, pistil & stamens, but as an union of modified leaves.

It were folly, however, to imagine that Goethe had as comprehensive an understanding of morphological principles as we possess at the present day. His most ardent admirer will find him wonderfully abstruse and befogged on comparatively simple points, as when he endeavors to establish a

direct analogy bet the metamorphoses of plants and animals

Some german naturalists have availed themselves of these few weak points to deny the pol all proper appreciation of morphological doctrines, and others have sought to detract from the merit of his work by disputing his priority of discovery. Linnaeus & Wolff. it has been claimed, anticipated Goethe's theory of plant metamorphosis Linnaeus claim rests upon the one phrase "prolepsum florum et foliorum idem est": which is at most but a faint perception of the doctrine and not a demonstration. As for Wolff G. has acknowledged his priority. but was the first also to reveal that author's famous work after he had written his own treatise.

Since the poet arrived at his conclusions independently of each another can not in no way his priority of discovery diminish the worth of his achievement! Will you underrate Darwins work because Wallace reached the same conclusion. or would any one call Darwin to task, if, as will be remembered, he was anticipated in several points by the author of Faust.

Men of science however, did not bestow upon Goethe the consideration they would have given the humblest scientific tyro. The anatomists will not be convinced by his treatise on the intermaxillary bone and Camper returns the manuscript commending the splendid handwriting, but suggesting that a better Latin style would be desirable! For the anatomist as for the popular mind, it was difficult to conceive that the author of Werther & of Egmont should work and delve and seek the hidden treasures of anatomy.

The scalpel was but a means to accomplish an end. It was guided by the intellect of the poet who was studying Nature not so much for the sake of its details as to use these details to make grand generalizations concerning its phenomena. Surely, there is no such impassable gulf between Goethe the poet whose works teem with wonder and admiration for Nature's laws & Goethe the man of science, who finds in them the realization of sublime principles. He

The further consideration of such principles pursued upon, and verified by the closest study led to his third important discovery — to the theory that the skull is in a certain sense a repetition of the spinal column. His right to the priority of discovery was once more severely contested and claimed by no less a man than Oken. A remarkable coincidence in the occasions on which both these men claim to have reached their conclusions has helped to embitter the disputes. I am willing to credit both accounts of this coincidence, would give but another proof that the morphological doctrines which were then 'in the air' must inevitably have led to these conclusions.

Though Oken was the first to announce his results, letters which have been recently published, written by Goethe prove beyond doubt that sixteen years before Oken's publication appeared he received and expressed his idea of the vertebral theory of the skull.

The theory itself has been subjected to the severest criticism. Yet, whatever be the fate of the theory, the creed which gave it

bird, has already exercised an important influence on modern scientific ideas and still promises a long and vigorous life.

This World-Idea was peculiarly Goethe's own; but did his wonderful genius allow him to anticipate those grand results which have reached their climax in the steady progress of the Evolution theory? Nay, it has been asked, Was Goethe a Darwinian? And the replies have been various.

No single thought is more constantly expressed throughout his scientific writings than that there is nothing permanent in nature. He would not have expressed more clearly his dissent from the prevailing notions of his day. Will not, perhaps, the tendency of his thought give some clue to his positive convictions?

The only system of philosophy which had a decided influence on the development of his mind was that of Spinoza. His pantheistic doctrines urged him to seek in every group of organic phenomena the underlying substance—the type. But in this type

an ideal type, an imaginary Urbild, a mere abstraction, or is it synonymous with the ancestral form in modern Darwinism? Goethe's type can not be ideal, for it grows, develops, and is modified by the condition of its environment. It has been urged, however, that he uses the type as a mere matter of convenience — an ideal standard. True, but it is only unfortunate, then, that he uses the same word for two distinct ideas. Moreover, the most thoroughgoing Darwinian would not hesitate to speak of a type or plan according to which animals are formed. Does not Goethe corroborate modern thought when he infers that in their simplest forms, the animal and plant type are not distinct, and does he not declare himself opposite to the purely teleological view of nature when he requires that we should ask not why an animal has a certain organ, but how it has obtained it? In this regard Goethe's genius in science was evidently among the first to grant the differentiation of organisms from a simpler type. Does

he also recognizes the principles which govern this differentiation!

The adaptations and modifications of organs under varying conditions of environment — the changes produced in them by use and disuse he discussed with considerable precision; but he has failed to see that these are the mere agents and not the causes of this differentiation. The probable explanation of the causes has been deferred to our own time; and we may well be proud that Darwin has made a great step toward the solution of this problem in presenting his theory of Natural Selection — a selection working in all organic creation by reason of a struggle for existence.

So much the greater Darwin's merit, and more the lof Goethe's fame!

What a wonderful picture does Germany's greatest poet present — A careful student of nature, Wasche, a

learned man of science, and a thorough philosopher. An entity unto himself.' In his words, as in his view of nature, we see:

'Wie alles auf ein Ganzen weht
Eins in dem Andern wirkt und lebt.'

ON ARRESTED CEREBRAL DEVELOPMENT, WITH SPECIAL REFERENCE TO ITS CORTICAL PATHOLOGY[1]

B. SACHS, M.D.

[*New York*]

Our knowledge of the pathological substratum of the various forms of mental derangement is still very imperfect. In the majority of cases, there may be no marked changes in the structure of the brain; or, if there be any changes at all, they are entirely beyond our ken, and cannot be made out by our present methods of investigation. As mental pathology is in its infancy, it is but natural that we should first seek for structural changes in those conditions in which the departure from the normal is greatest, in which the mind is disturbed, as a whole, and not merely with reference to a single part or faculty; though I shall at once declare my belief that derangement of a part of the mind means disorganization, more or less complete, of the entire mental mechanism.

While we are even now in possession of many facts concerning the morbid structural changes in dementia paralytica, changes that accompany the complete *dissolution* of a fully developed, and once normal mind, we have busied ourselves but little with the morbid changes that often affect the brain, and consequently the mind also, when both are yet undergoing the process of *evolution*. These cases of retarded development, of idiocy, of mental imbecility, call them what you will, seem to me to possess a deep pathological and physiological interest. From the pathological changes found in these cases of extreme mental defects, we are entitled to draw an inference regarding the normal function of those nervous elements here found deficient, and we may well argue with regard to such broad facts as an absolute lack of mentality, although it may be a long time to come before we shall be able to explain the morbid mechanism underlying fixed delusions, hallucinations, and the like, or to state exactly what the structural changes are in paranoia, in circular insanity, and in other grave mental troubles.

The condition which I have the privilege of discussing before you to-day represents not only such changes as come about in the process of evolution, but represents changes of the earliest period of infantile development.

Much has been written upon idiocy and allied conditions from the clinical point of view, but pathological and pathological-anatomical observations are surprisingly few and far between. And those who give gross morbid changes fail to refer to the histological changes either in the cortex or other parts. Thus Bourneville,[2] who has made an excellent contribution to the study of this subject, refers in only one of five cases to changes in the cortex. Brückner[3] has

[1] Read before the Amercian Neurol. Assoc., July, 1887.

Reprinted from the Journal of Nervous and Mental Disease, 14: 541, 1887.

[2] Bourneville, "Sclerose tubereuse des circonvolutions cerebrales." Arch. de Neurologie, vol. 1.

[3] Brückner, "Ueber multiple tuberöse Sklerose der Hirnrinde." Arch f. Psych., vol. 12.

given the most detailed account of the histological changes in the cortex with which I am acquainted. His was a case of what is known as tuberous sclerosis of the cortex, and concerned a patient 22 years of age. The pathological changes underlying these conditions of idiocy are undoubtedly as varied as the clinical manifestations themselves; for the present we designate these affections by broad clinical terms; later on we may be able to differentiate between them, and to give to each condition its proper pathological designation. Looked at in this way, the title of my paper is altogether too comprehensive. The changes which I have to report upon to-day are a few of the many changes which may give rise to similar clinical mental phenomena.

Before presenting the history of the case, I must acknowledge my indebtedness to Dr. I. Adler, of New York, through whose kindness I was enabled to observe the case closely, and with whom I shared the responsibilities of treatment; and to my friend, Dr. Van Gieson, who was kind enough to supply me with normal material of the same age for comparison, and who, during an unexpected absence from the city, assisted me in the work of cutting and staining.

The following is the history of the case: The little girl S., who was but two years old at time of death, was the first-born of young and healthy parents. In the families of both parents insanity is not unknown; on the mother's side there is a strong hereditary predisposition to mental disease, and several near relatives of the father have developed various forms of insanity within recent years. During the fifth month of pregnancy, the mother was thrown out of her carriage, but did not sustain any serious injuries; the child was born at full term, and appeared to be a healthy child in every respect; its body and head were well proportioned, its features beautifully regular. Nothing abnormal was noticed until the age of two to three months, when the parents observed that the child was much more listless than children of that age are apt to be; that it took no notice of anything, and that its eyes rolled about curiously (there was evident nystagmus). Allowing for some very slight vacillations, the child remained in practically the same condition up to time of death. The condition was characterized as follows: The child would ordinarily lie upon its back, and was never able to change its position; muscles of head, neck, and back so weak that it was not able either to hold its head straight or to sit upright. It never attempted any voluntary movements; movements that were made were in obedience to peripheral stimulation. All the muscles were extremely flaccid; all reacted perfectly to both forms of current. The child would close its hand upon the finger of the examining person, but objects placed in its hands were quickly dropped. The child as it grew older gave no signs of increasing mental vigor. It could not be made to play with any toy, did not recognize people's voices, and showed no preference for any person around it. During the first year of its life, the child was attracted by the light, and would move its eyes, following objects drawn across its field of vision; but later on absolute blindness set in.

Dr. Knapp, who made several ophthalmoscopic examinations of this case, reported the following unusual condition, at the seventeenth meeting of the Heidelberg Ophthalmological Society. The report may be found in the Proceedings of this meeting. Dr. Knapp there says: "Child two to three months;

nystagmus vibratorius; pupils contracted as is usual with children at this age. Media clear, optic nerve discs pale. Fovea centralis, of a cherry red color, was surrounded by an intense grayish-white opacity. This opacity was most distinct in the vicinity of the fovea centralis, and for some little distance around it, but faded away gradually into normal retinal field."—Dr. Knapp at first gave a favorable prognosis, except as regards central vision, more particularly as there appeared to be for some time a slight improvement in vision. He could not then, and is not now ready, to give an explanation of this condition.

But two cases of this sort of retinal changes had thus far been reported, by Magnus and Goldzieher, and neither of these authors has any explanation to offer. Dr. Knapp, in private conversation, hinted at a developmental defect. Unfortunately, the eyes could not be removed after death. Dr. Knapp empowers me to add that "a further examination in May and June, 1886, revealed great changes. Child totally blind, optic nerves completely atrophied (discs as white as paper, with scarcely a trace of blood-vessels). Macula lutea essentially as before."

By way of anticipation, it may be remarked that numerous longitudinal and vertical sections of both optic nerves were variously stained and examined, but that no morbid changes could be made out. Blindness must, therefore, have been due either to the retinal changes, or to the deficient cortical condition, or to both.

Hearing seemed to be very acute; there was unusual hyperexcitability to auditory and tactile impressions; the slightest touch and every sound were apt to startle the child. The child never had convulsions, not even while teething; no marked rigidities at any time. The child never learned to utter a single sound; if left to itself it would occasionally make a low gurgling noise. Bodily functions normal, excepting the frequent recurrence of bronchial troubles and feebleness of its digestive powers. At the age of one it had a severe attack of diphtheria from which it rallied in the course of a few weeks. The child developed unusually high fever with every disturbance, however slight, of its bodily functions. In the way of treatment nothing was recommended but careful nursing and feeding, tonic treatment with malt and the like; phosphorus was given in small doses for a time, and the peripheral muscles and nerves were alternately galvanized and faradized, more in the hope of exciting cerebral activity in a reflex way than of benefiting the nutrition of the flaccid parts.

There were no distinct evidences of inherited or acquired syphilis and none of rachitis.

During last summer (1886), the child grew steadily weaker, it ceased to take its food properly, its bronchial troubles increased, and finally, pneumonia setting in, it died August, 1886.

Immediately after its death, the child was brought to the city, and yet twenty-nine hours had elapsed before the autopsy could be made.

Autopsy.—The autopsy was confined to an examination of skull, brain, and abdominal viscera. The body was in a state of extreme emaciation; all muscles relaxed. The skull was thick, and skull cap unusually heavy. Outer and inner surfaces smooth and showed no unusual appearances or impressions. Skull

symmetrical; left frontal fossa a trifle deeper than right; large fontanelle very nearly ossified. A large organized clot was found in the superior longitudinal sinus; there was some thickening of the dura to either side of the sinus, some slight adhesion over the upper portion of the precentral and over the left temporal convolution, but even here and over the entire surface of the brain the pia could be easily removed without injuring the parts below. There was an œdema of the entire convexity; unusual pallor of the convolutions; no marked increase of the fluid in the lateral ventricles. Freed of its dura, the brain weighed exactly two pounds (one thousand grams). Blood-vessels appeared normal and had normal distribution. I may state at once that the cortex was hard to the touch, and that the knife grated in removing a small portion of the cortex for immediate examination. This grating was due to small calcified plates. On superficial inspection, the great breadth of the fissures, the corresponding narrowness of the convolutions, and the unusual exposure of the left island of Reil were very apparent. A detailed examination of the larger ganglia, of the pons, medullary, etc., will be made and will be reported upon later on.

The spleen was enlarged and the liver hard, but no evidences of hereditary syphilis.

Examination of brain. The brain was immersed at once into Müller's fluid, and as soon as hardened the brain surfaces were photographed.[4] By comparison with the paper[5] which our retiring president read last year, you will recognize certain departures from normal fissuration which are indicative of inferior brain development.

Examination of brain surfaces. Left hemisphere, outer surface. (Plate I.)

The most striking features are the great depth of all fissures, and the comparative simplicity of fissuration, particularly in the frontal lobes; the great exposure of the island of Reil due to the retraction and narrowness of the surrounding convolutions. The central fissure (*c*) is bifurcated and is clearly confluent with the Sylvian fissure which is broad and long. The first temporal fissure (*t.* 1)—supertemporal, Wilder—would be continuous high up into the parietal region, but for a slight bridging convolution. The parieto-occipital fissure is unusually distinct and in the occipital lobe the three fissures are easily traced. In the frontal lobe, the first and second frontal fissures are well marked, while the second forms the long branch of a zygal formation according to Wilder. The convolutions appear alternately narrowed and broadened; this is particularly true of the first temporal and precentral convolutions. The gyrus angularis is scantily developed.

The mesial surface of left hemisphere exhibits the confluence of the parieto-occipital, the calcarine and hippocampal fissures. The collateral fissure of Wilder well marked. The calloso-marginal fissure well defined though shallow. The præcuneus massive, the cuneus of normal size.

Right hemisphere—*outer surface.*

[4] I am indebted to Mr. O. G. Mason for the original photographs, but one of which is reproduced in this article, all four photographs were exhibited at the meeting of the Association.

[5] C. K. Mills, Presidential Address, *Journal of Nervous and Mental Disease*, vol. 12, 1886.

Here the conditions approach much more nearly to the normal. The island of Reil is scarcely exposed; the fissure of Sylvius of normal breadth and length; the central fissure is confluent with the fissure of Sylvius. The first temporal convolution is *continuous* into the parietal region, and there is a distinct though very narrow angular gyrus. Wilder's interparietal fissure is distinct; in both the occipital and frontal lobes, three typical fissures can be made out; there is an undoubted medifrontal (Wilder) fissure which could not be traced on left side. The parieto-occipital does not form as distinct an indentation as on left outer surface.

Median surface.—The parieto-occipital, calcarine, and hippocampal fissures are confluent; the collateral fissures well defined; the entire mesial surface is divided into small blocks by numerous secondary fissures. Cuneus and præcuneus of normal development.

Microscopical examination of the cortex. The brain surfaces, after they had been thoroughly hardened in Müller's fluid, were cut up into small blocks for histological examination. Sections from the frontal lobes, the motor zones, the base of the third frontal convolution, from the first temporal convolution, and from the occipital apex of both hemispheres have been examined. The cuneus was unfortunately too brittle to permit of section cutting. From the portions thus far examined, it is fair to infer that the changes to be described affect equally every part of the brain surface. The plates herein given represent the changes as seen in sections from the first temporal convolution of the left side. These specimens were stained according to the acid fuchsin method, others were stained with Weigert's two hæmatoxylin methods, and with ammoniacal carmine. You will note that the cellular elements exhibit the same changes, whatever staining method we employed. On the drawing, most carefully made by Dr. Van Gieson, and in these specimens[6] the following conditions may be noted.

We are able to distinguish the external barren layer, the layer of small pyramidal cells, the layer of the large pyramids, and perhaps a trace of Meynert's fourth granular layer. Examining these sections, very marked changes will be observed in the structure of the small and large pyramid cells. In my search through the entire brain I have not come across more than half a dozen, if as many, pyramid cells of anything like normal appearance. The fewest large and small pyramid cells show well-defined processes. The contours are rounded, and the cell substance exhibits every possible change of its protoplasmatic substance. In some there are a distinct nucleus and nucleolus, surrounded by a detritus-like mass; in many the nucleus and nucleolus are entirely wanting. All these varied changes can be studied best with the acid fuchsin method; in Weigert preparations, the whole pathological cell mass takes up the stain deeply, and it is not always easy to distinguish the nucleus and cell-body. Glancing through the sections, you will also observe that a few of the cells turn their apices downward instead of upward, thus exhibiting a change to which Brückner refers as occurring in his case of tuberous sclerosis and to which no pathological significance is to be attached.

Plate III exhibits these changes under a very much higher power. In some

[6] Demonstrated at the meeting.

cells a partly normal and a partly pathological character of the cell-body is visible. In the neuroglia, I have not been able to prove any changes; there is certainly no sclerosis visible in any part I have examined. The white fibres have not undergone morbid changes, but on Weigert specimens they cannot be traced as far towards the periphery as in the normal cortex; the transverse fibres in the outer barren layer could not be made out. There is no evidence whatever of any previous encephalitic process. No infiltration around the blood-vessels; in fact no changes in any of the blood-vessels of the cortex. At the meeting, doubts were expressed whether there was not a paucity of blood-vessels. I have paid special attention to this point, and am now convinced, after examining a very large number of sections from every part of the cortex, that these capillary vessels are of normal calibre and as numerous as in corresponding sections of the normal brain. Nor is there any proliferation of the nuclei of these cells in the walls of the blood-vessels. We have then a simple change affecting the cells and possibly the white fibres only, and the question remains to be decided whether there is mere arrest of development, or an arrest of development the result of a previous inflammatory process. There is nothing in support of the latter proposition, and everything in favor of the former.

I cannot find any evidence of distinct degenerative changes in the cells, and it would seem to me that, if the process were one that had set in after the cells had already matured, we should find some, and many more cells than we actually do, exhibiting a more complete formation than any to be found on the specimens before you. You will note also that there were no gross changes such as are frequently held responsible for insufficient development: there is no evidence of hydrocephalus internus, of a general or a multiple tuberous sclerosis; no traces of a preceding encephalitis.

We have here an agenetic condition pure and simple, affecting the highest nerve elements. As to the cause of this agenetic condition, I am not willing to speculate. I repeat that syphilis is excluded, at least not proved, that there is strong hereditary predisposition to mental troubles, and that there is the etiological factor of traumatism in the case. As the fætal circulation is easily affected by the slightest disturbances, and the proper nutrition of the most highly differentiated organ of the body may in this way have become impaired, we cannot afford to overlook the factor of traumatism.

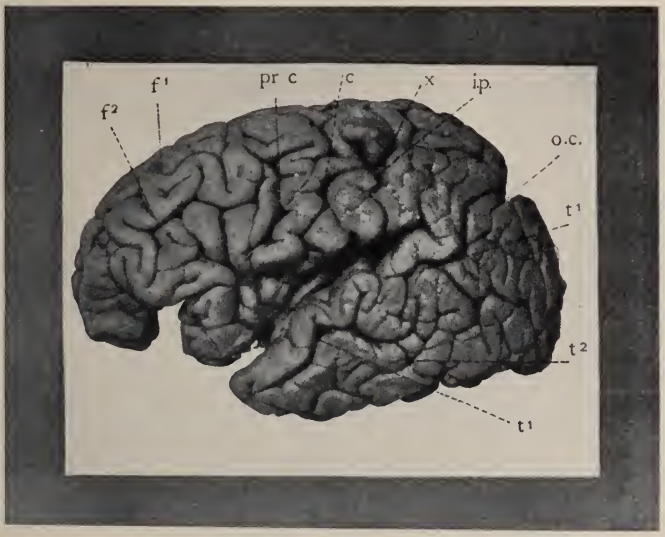

PLATE I

Outer aspect of surface of left hemisphere showing the exposure of the island of Reil, and great breadth of fissure of Sylvius.

X denotes region from which first block of cortical tissue had been removed for histological examination.

C, central fissure or fissure of Rolando.

prc, precentral fissure.

i. p, interparietal fissure.

oc, occipital; parieto-occipital fissure.

t^1, t^2, first and second temporal fissures.

f^1, f^2, first and second frontal fissures.

Other explanations in text.

PLATE II

× 70 diameters

Section from first temporal convolution; specimen stained with acid fuchsin; drawing made with especial reference to changes in the cells.

Divisions A, B, C, correspond about to layers of superficial neuroglia, of small pyramid cells and of large pyramid cells. Below C is fourth granular layer (Meynert).

It will be noted that with this low magnifying power, the changed appearance of the pyramid cells can be made out. The contours of the cells are altered, the pyramidal shape is often widely departed from; the cell body is altered, and occasionally shows distinct lacunae.

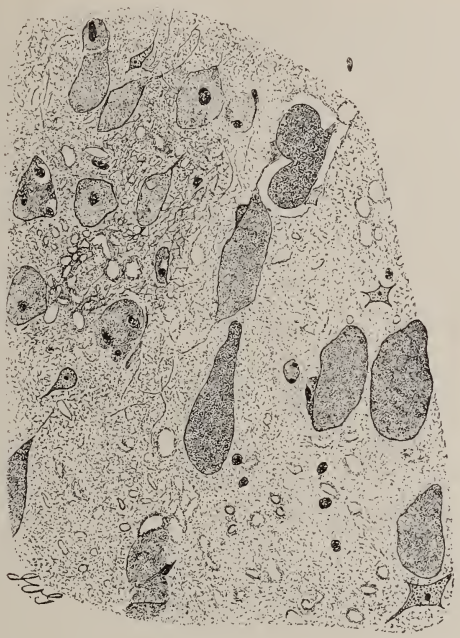

PLATE III

× 500 diameters

Section of first temporal convolution, representing a portion of division C under much higher magnifying power. Pyramidal cells have lost their normal shape. The cell body has a homogeneous but altered appearance; nuclei either absent or distorted; smaller cells and neuroglia cells with distinct nuclei; section of capillary vessels normal, in the upper right hand corner a distorted cell mass with pericellular space around.

THE FIRST NEUROLOGICAL DIVISION IN NEW YORK CITY—AT THE MOUNT SINAI HOSPITAL[1]

BERNARD SACHS, M.D.

My years of service at The Mount Sinai Hospital have meant so much to me that I yielded to the Editor's repeated bidding to tell of the rôle this Hospital played in the development of Neurology in this City.

I am going to tell the story and if my own person is too much in evidence (*Quorum pars magna fui*), sorry, but facts are facts. In the late Seventies and early Eighties of the last century, Neurology had already made a distinct impression on medical science here and abroad. Charcot, Hughlings Jackson, Erb, Weir Mitchell, William Hammond, Seguin, Spitzka and Starr had made fundamental contributions to this rapidly developing specialty, but General Medicine, as it does to this day, tried to hold its child in check and to deny its rights. No private (voluntary) hospital had established wards for nervous diseases. The General Medical Attending was supposed to know it all. Discussing this question with Abraham Jacobi as far back as 1885, I asked him whether he realized that a knowledge of Neurology has to be acquired and does not come by intuition. He pardoned my boldness and in spite of this frontal attack, we were good friends many years thereafter.[2]

My first dispensary work (1884) was done as a Volunteer Assistant in the Surgical Division, under Arpad G. Gerster, in the old German Dispensary at Second Avenue and Eighth Street. I doubt whether Gerster thought highly of my surgical ability, but it helped to make me known to him and he became interested in what I was doing. He was fully alive to the important questions of cerebral localization and after a year or two invited me to advise him in the old Lexington Avenue building of The Mount Sinai Hospital regarding cases of epilepsy and brain tumor. It was Gerster's appreciation of neurological science that was largely responsible for my appointment as "Consulting Neurologist" to The Mount Sinai Hospital in 1893. For many years there was the friendliest sort of coöperation between Gerster and myself at the Hospital and at the Polyclinic where both of us were active. Conjointly we published articles on the Surgical Treatment of Epilepsy in the *American Journal of Medical Sciences* in 1892 and 1896; also an article in the *Deutsche medizinische Wochenschrift*, 1896 (good old days!). In the latter article we reported a critical analysis of the result in nineteen cases—a significant series in those pioneer days, and as I reread the conclusions they may even, to this day, stand "approved as read."

This association with Gerster made my consulting work of great interest to me and, I believe, of special service to the Hospital. Although I had been made Professor at the Polyclinic in 1888, four years after I entered practice, and had clinical opportunities at the Polyclinic with Gerster, Wyeth, and Landon Carter Gray, and at the Montefiore Home with Dana, Harlow Brooks, Fraenkel

[1] Reprinted from the Journal of The Mount Sinai Hospital, 6: 303, 1940.

[2] I was particularly proud that I succeeded him in the Presidency of the Medical Board and that both of us had been President of the New York Academy of Medicine.

and others, and I should have been flattered by the President's report (1893) (in which he stated that "Dr. S. Lustgarten had been appointed Consulting Dermatologist and Dr. B. Sachs Consulting Neurologist, two new positions created this year"; that "no separate wards or beds are assigned for these departments the object being mainly to afford consultation with these *eminent* specialists for the benefit of certain classes of patients in the Hospital"), yet I was not happy and soon felt, what I have said in later years, somewhat facetiously, that in a hospital a "consulting" physician is a physician who is never consulted. I was willing to be demoted to Attending Neurologist, if special wards would be assigned to me. Here again, Gerster and several good friends among the Directors were of help to me; and finally in 1900, the Neurological Service (for years never more than six male and six female patients) was created at The Mount Sinai Hospital; and the first special Neurological wards in any of the larger private hospitals of New York City were established. I must add, in justice to my colleagues on the Medical Board, that even as Consulting, I was made a member of the Board and almost immediately made a member of the Board of Examiners, together with Janeway and Arpad Gerster. I tried to be fair to the applicants, but some soon discovered that I gave preference to the candidate who could write prescriptions proving that he had an inkling of Latin forms and terms.

In those days, Janeway, Rudisch, Alfred Meyer, Heineman were the Attending Physicians; Gerster, Wyeth, Stimson and Fluhrer were the Attending Surgeons; Paul F. Mundé was Gynecologist (preceding my friends Joseph Brettauer and H. N. Vineberg); Gruening was Ophthalmologist and Aural Surgeon. He was followed several years later by Charles H. May and Carl Koller. Nathan Brill and Manges were appointed Attending Physicians, while Koplik was appointed Attending to the Children's Service. It may recall still more vividly that time "long ago" if I state that Howard Lilienthal had just appeared on the horizon, having been appointed Assistant Attending Surgeon in 1895 and raised to the rank of Attending Surgeon in 1899; A. A. Berg and C. A. Elsberg were Adjunct Attending Surgeons; Edwin Beer, having graduated from the House Staff in 1902, was far from the top. All of them have since "arrived," and, to my sincere regret, some have passed to the great beyond.

I have happy recollections of the Medical Board meetings with Janeway and Gruening, the latter acting as Secretary to the Board, and of the occasional visits from the President, Mr. Isaac Wallach and, later on, and for many years, of visits from Mr. George Blumenthal.

Once I was on a par with other Attending Physicians and Surgeons, I had smooth sailing. Even Jacobi allowed that Neurology deserved to be on the map and all the others referred cases freely to the Neurological Service.

While I had been enabled to utilize the splendid material of the Polyclinic, with which I had been connected since 1886, and of the Hospital for Ruptured and Crippled (through the courtesy of Gibney), it was a welcome enlargement of my field of activity to have a special service in which neurological cases could be examined most carefully, employing and testing always the newest

diagnostic and therapeutic methods. I felt that the chief aims of such a service should be the considerate treatment of the patient, making use of the most recent methods, the training of an adequate House Staff and, above all, the development of a group of able associates and assistants who would be certain in the course of time to contribute materially to the advance of neurological science. Incidentally, I stressed the importance of the doctor looking neat, being scrupulously clean, using good English, and articulating distinctly. I feel that I may claim to have succeeded in these various aims and am certain that I gave the staff every opportunity for independent research and publication.

While I was deeply interested in new procedures and laboratory methods, the guiding principle was that bedside observation was of the greatest importance—that the diagnosis should be made at the bedside—that laboratory methods might be considered supplemental and corrective, but must not and cannot displace clinical observations based upon anatomical and physiological knowledge of the organs involved.

Whenever special medical or surgical knowledge was required, we called in special authorities in the Hospital. Another principle adhered to from the beginning was the encouragement given the House Staff and the Assistants to study each case independently, to present the report on official rounds, and receive credit or well-meant criticism in the presence of the Staff and some visitors.

From the fact that some of my former staff have commented upon the advantage to them of my methods, I may feel that the service was a success. Parenthetically, I may add that one reason why I was specially concerned with the opportunities given my associates and assistants was that in my earliest years I was made unhappy while I was associated with a physician who never got away from the idea that the younger man knew nothing and that he knew it all. I cannot mention all the former assistants and associates who were subject to my tyrannous treatment, but the general calibre is indicated by names well-known at this day: William Hirsch and I. Abrahamson in 1904; a little later Strauss, Friedman, Grossman, Keschner, and Wechsler. Globus was added to the group, and his neuropathological laboratory has added greatly to the value of the work done in the Neurological Division. Many others were active in the Dispensary. If there was any fault at the time, it was that the Out-patient Department Service was not intimately linked with the Hospital, although all the men were privileged to make rounds three times a week (9–11 a.m.) with the "Chief" and his aspiring Adjuncts and Assistants. Goodhart, Hausman and others were regular in attendance.

The Service was active from 1904 (in the present Hospital) until 1924, when I was retired because of age, and no doubt properly so.[3] The Ward facilities had been enlarged in 1922, when we moved into the present wards which had been established by my two brothers, Samuel and Harry Sachs, and dedicated to the memory of our parents.

Let me refer to some of the special work done in the Clinic. The first considerable epidemic of poliomyelitis was carefully studied; a few years later epidemic

[3] Although I have had some of the most active years in professional work since 1924.

encephalitis had our closest attention. At all times we maintained a critical attitude in order to ascertain the exact truth and not fall victim to passing fancies. Syphilis of the nervous system had our special interest. It was the period of the Salvarsan therapy and of the Swift-Ellis treatment. We maintained our critical attitude; did not favor the general use of the latter and, as has been shown since, were correct in our conclusions. Just so in our years of study of the Wassermann reactions of blood and cerebrospinal fluid, we made very liberal use of the tests, but claimed that there were other equally important indications of constitutional syphilis and that a negative Wassermann did not exclude syphilis, especially if the pupillary reflexes—or the absence of them—indicated previous specific infection. In this work, Doctor Kaliski, who made rounds regularly with us, was very helpful. One of my former assistants reminded me only a short time ago of the repeated question I put to Kaliski—"Are the Wassermanns all positive or all negative this week?"—showing that we were not completely overawed by these tests, much as we esteemed them. I hold it to be one of the chief functions of such a Hospital service to become acquainted with all newer methods of diagnosis and treatment, and to exercise sound critical judgment in evaluating and applying them.

During these years, the Service provided ample opportunities for studies on acute infectious myelitis, on tumors of the brain and of the spinal cord—wherein we had the support of the Neurosurgical Division and especially of Elsberg, A. A. Berg, and later on of Ira Cohen—on various forms of paralysis agitans, notably after the study of epidemic encephalitis, on the muscular dystrophies, on erythromelalgia, scleroderma and other rare vasomotor conditions. This Service was, for a long time, the only one in the City to provide bedside observation of acute neurological diseases. At the Montefiore Hospital, chronic cases were studied carefully, but the Neurological Institute had not yet been established and Bellevue had not yet opened special neurological wards. It is a great personal satisfaction to me to know that the Neurological Division became, and has remained, an integral part of a great Hospital. I acknowledge the good work done by my successor, Strauss, and now by Wechsler.

I feel that with great opportunities come great obligations and I trust that in the impending development, especially of the newer electrical and electroencephalographic methods, and also in view of the recent advances in the chemistry of the brain, and of the impending era of chemotherapy, the Mount Sinai Neurological Division will occupy a prominent rank. I also hope that in order to do full justice to the study of the neuroses and the neuropsychoses and to study them critically without being victimized by any one school of thought, this Service may be developed into a Neuropsychiatric Service, in which organic neurology will always play the important and fundamental rôle which it holds by right in the latter day development of neurology and psychiatry.

TUMOR OF THE ITER AND FOURTH VENTRICLE ASSOCIATED WITH A MENINGO-MYELOCELE AND ABSENCE OF THE CEREBELLUM IN AN INFANT OF FIVE WEEKS

BERNARD J. ALPERS, M.D.*

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INTRODUCTION

The occurrence of a large tumor in the iter and fourth ventricle of a five weeks' old infant with a meningo-myelocele and cerebellar aplasia appears to warrant recording for the light which it may shed on the problem of origin of some brain tumors.

CASE REPORT

History. This five weeks' old infant was born of normal parents by normal delivery and weighed six pounds at birth. The immediate post-natal birth history is not recorded except that it was noticed that the infant had an enlargement at the back of its head at birth. It was for this deformity that she was brought to Dr. C. H. Frazier and admitted to the University of Pennsylvania Hospital on June 27, 1932.

Examination: A mass the size of a lemon was noted, which protruded in the occipital region and extended down over the neck of the infant. The mass was firm and the skin over it was not covered with hair.

Neurological examination was said to be negative.

Roentgen examination of the skull revealed a defect in the occipital bone and a soft tissue mass in the occipital region.

Operation. The patient was operated on by Dr. Frazier on July 7, 1932 and the meningocele completely removed. Death ensued several hours after operation.

Necropsy Findings: There was a patent ductus arteriosus and a patent foramen ovale, but apart from this the gross and histological studies of the viscera were negative.

Gross examination of the *brain* revealed the following findings: The cerebral hemispheres showed nothing unusual. The most striking feature of the uneut brain was an almost total absence of the cerebellum except for a small portion of remaining tissue which could be identified as inferior and superior vermis and paraflocculus. Nothing was seen of the cerebellar hemispheres. The inferior olives could not be seen on gross sectioning, nor could foeal areas of cerebral atrophy be identified (fig. 1).

Sectioning of the brain revealed a tumor first seen as a small nodule extending into the iter in the posterior part of the mesencephalon at the level of the inferior colliculi. The tumor also extended backward into the pontile portion of the fourth ventricle and seemed to terminate in the anterior third of the fourth ventricle in the medulla (fig. 2). It extended therefore from the posterior portion of the mesencephalon to the anterior portion of the medulla, extending into the iter and filling part of the fourth ventricle. It appeared not to infiltrate the brain tissue but to be attached to the ventricular ependyma. The medullary vela appeared to be thickened. A mild hydrocephalus was present involving the lateral and third ventricles.

Histological study of the specimen removed at operation revealed a meningo-myelocele.

Study of the tumor revealed the fact that it lay entirely within the iter and fourth ventricle. It was attached to ependyma in the mesencephalic, pontile, and medullary areas in localized portions, the bulk of the tumor lying within the ventricular cavity without

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ependymal attachment. It appeared to take its origin from the collicular region of the mesencephalon, to which the tumor was attached by a thin pedicle. The pedicular attach-

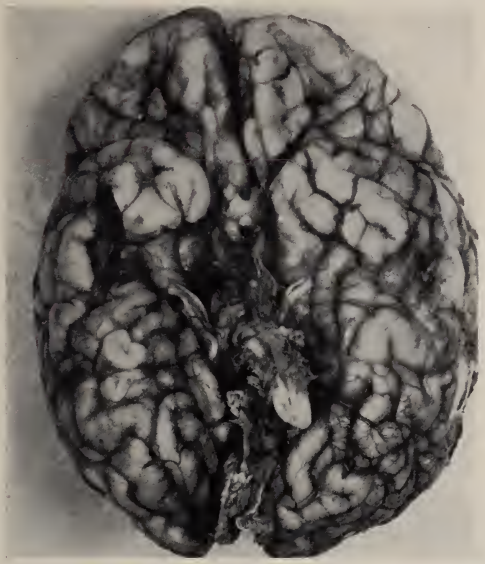

FIG. 1. Base of the brain showing the complete absence of the cerebellum

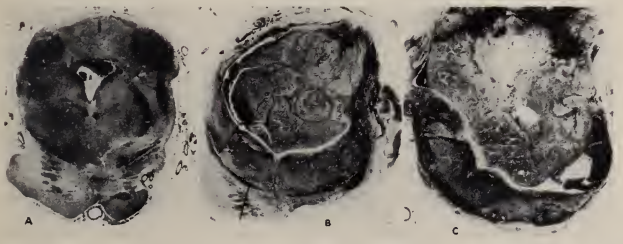

FIG. 2. Myelin sheath stains of the brain stem showing in A the small tumor projecting into the ventricle, attached by a small pedicle to the collicular region; in B the tumor fills the fourth ventricle and has a more extensive connection with the brain stem; in C it is even more extensive. In B and C is seen the entire extent of the cerebellum.

ment was covered with ependyma. The area of transition from the colliculus to the tumor was of interest: first came a congested and rarefied area showing a loss of ganglion cells

and a moth-eaten appearance, then the pedicular portion covered by ependyma which was thrown into folds, and then an abrupt transition into tumor tissue.

The tumor itself was found to consist of small cells of an undifferentiated type, with small round nuclei containing heavy granules of chromatin, giving the cells a lymphocytic appearance. Among them were scattered astrocytic nuclei and strands of collagen. The tumor cells resembled closely the granule cells of the cerebellum.

DISCUSSION

The incidence of tumors in newly born infants is difficult to ascertain, since a review of the literature fails to reveal statistics concerning this point. Studies of the occurrence of brain tumors in infants under 1 to 2 years of age are available (Bailey, Buchanan and Bucy (1); Stern (2)) but no reference can be found to the congenital occurrence of tumors in infants. The problem is important since cases such as the one described herein appear to lend support to the congenital origin of some of the infiltrating tumors of the brain. Canavan and Hemsath (3) found a small tumor nodule in the mid-olivary area "springing from the clothing cells of the ventricle." The tumor was adherent to the ependyma from which it appeared to arise. Their tumor was found in a premature infant who died seven months after birth. Bravne (4) describes a tumor in an infant of fourteen weeks, the tumor being an infiltrating glioma in the left cerebral hemisphere.

Further indication that the tumor here reported was of congenital origin is given by the occurrence of other brain anomalies, such as the cerebellar agenesis and the occipital meningomyelocele. The cerebellum was almost completely absent except for small fragments of the vermis and the paraflocculi, and there was failure of myelination of the cerebellar fibres in the basis pontis.

Despite the apparent connection with the ependyma of the ventricle, the tumor structure resembled more closely the cells of the granular layer of the cerebellum.

SUMMARY

1. A tumor lying within the posterior part of the iter and filling part of the fourth ventricle was found in a five weeks' old infant who had also cerebellar agenesis and a meningomyelocele in the occipital region.

2. The case appears to lend support to the evidence in favor of the congenital origin of some brain tumors.

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REFLECTIONS AROUSED BY AN UNUSUAL TUMOR OF THE CEREBELLUM

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In looking through our pathological material incident to moving into new quarters we came upon an unusual tumor of the cerebellum situated in a region rarely involved by tumor, or any other pathologic process for that matter, the anterior part of the vermis. It started us to thinking about the cerebellum, its structure, its function and the possibility of differentiating the symptoms and signs resulting from destructive lesions of its various parts. Only if it were possible to do so could one ever hope to localize accurately such a tumor as we were contemplating.

SARCOMA OF THE ANTERIOR VERMIS

Case 1. This tumor was situated in the superior part of the vermis, adherent to the inferior surface of the tentorium (fig. 1). The lobulus centralis was only compressed but the culmen was largely destroyed, only the anterior half of the anterior leaflet remaining intact. Posteriorly the nodulus and uvula were intact, the pyramis somewhat compressed, the declive almost completely destroyed. The tumor had not simply compressed the anterior lobe but was actively invasive and destructive. It extended about 1.5 cm. to either side of the midline.

The tumor was removed from the brain of a young man of 23 years, referred by Dr. Howard E. Dorton of Oak Park, Illinois. He was admitted January 11, 1938. The personal history was not important. His mother died of tuberculosis.

About December 7 he began to have severe frontal headache. This came on in spells accompanied by dizziness and stiffness of the neck. On December 17 he had a severe headache, became dizzy, fell and could not walk for a few minutes. His eyesight began to fail. On December 20 a lumbar puncture was performed; the fluid was under pressure and straw-colored. On December 21 he became stuporous. On December 24 he began to have projectile vomiting. About January 2 it was noted that he squinted. His neck was stiff and he had pain in the back of the neck when he lifted the head. On this date he was seen by Dr. Howard Dorton, who found that his optic discs were swollen. He made a diagnosis of brain tumor and sent him to this hospital.

When admitted he was incontinent and stuporous. General physical and laboratory examinations were negative. His neck was stiff, his head was retracted and he complained when it was manipulated. The optic discs were elevated 3 to 4 diopters. Both external rectus muscles were weak. There was no nystagmus. There was a slight left facial paralysis, interpreted as being of central type. Stereognosis was thought to be disturbed in the left hand. There was no definite asynergy of the hands. The patient could not walk, nor even stand up. The tendon reflexes were brisk. There was a positive Babinski sign on the left side, doubtful on the right. The abdominal and cremasteric reflexes were present bilaterally, weaker on the left side.

The patient was thought to have a right fronto-parietal tumor. On January 13, 1938, a right bone flap was reflected. The brain was tense. The ventricle was found to be dilated; the fluid was clear. The tension being relieved the wound was closed without making a decompression.

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[1] From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine, Chicago, Illinois.

He did not improve and slowly became more stuporous. On January 22 a left subtemporal decompression was made. The left ventricle was found to be dilated and clear cerebrospinal fluid was obtained from it.

His condition did not improve. He died on January 30. Necropsy, restricted to the head only, disclosed the tumor already described.

Microscopically the tumor was composed of small cells with scanty cytoplasm and oval nuclei. Mitoses were numerous. The cells near the numerous vascular sinuses were healthy but there was extensive intervascular necrosis, in places organized into dense collagenic scar. Among the neoplastic cells were numerous strands of reticulin radiating from the blood vessels. The tumor was destructive and had distorted the surrounding cerebellum but slightly. It had evidently arisen from the leptomeninx and invaded the subarachnoid spaces widely over parts of the cerebellar cortex which appeared grossly to be uninvolved. In the parts of the cerebellar cortex which were not destroyed the Purkinje cells were healthy and doubtless functioning. The tumor was a sarcoma (24) of lepto-

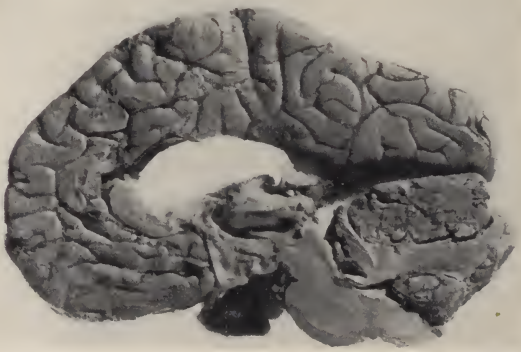

FIG. 1. Case 1. Tumor (sarcoma) invading the anterior lobe of the cerebellum, destroying the culmen, also the declive

meningeal origin, which is not surprising, since the patient was beyond the usual age-range of the gliomatous tumors of the cerebellum.

The pyramidal signs which this patient had were doubtless due to compression of the pyramidal tracts; even astereognosis may be produced by cerebellar tumors, through the same mechanism (12) of compression of the lemniscus.

The tumor is unusual, therefore, in both structure and situation, but the problem in which we are primarily interested is whether the location of this tumor should or could have been determined before operation.

FUNCTION OF THE CEREBELLUM

Our knowledge of the two great suprasegmental gray masses, the cerebral cortex and the cerebellar cortex, is still far from complete. Much the same controversies have raged concerning their functions, between those who believe that they act as a whole and those who believe that there is localization of

function. The great similarity of finer structure in the various regions of the cerebral cortex leaves little doubt that there is some mode of action common to the greater part of the cerebral cortex even though no one has been able to define it clearly. The practical identity of the finer structure of the cerebellar cortex throughout its extent suggests even more strongly some common mode of action of the entire cerebellar cortex, yet physiologists have been even less able to define its nature.

In the case of the cerebral cortex, even in the six-layered iso-cortex, differences in structure exist within the generally uniform pattern permitting it to be mapped into areas some of which have been proven to coincide with areas of special function. This is not true of the cerebellar cortex which, until recently, has defied all efforts to analyze it into areas of specialized function.

Insight into the focal functional differentiation of the cerebellum began to come first from comparative anatomy (7, 16, 24a, 25). The physiologists have followed this lead with illuminating studies, especially on the primates. The clinic and pathologic laboratory had less to offer since the usual vascular lesions, on which our knowledge of cerebral function is largely based, rarely involved the cerebellar cortex alone but nearly always included parts of the brain stem. Although traumatic lesions of the cerebellar hemispheres showed us clearly the syndrome of the ansiform lobe in man (23), and the frequent malignant tumor of the posterior vermis in children pointed toward the syndrome of the flocculonodular lobe (2), the syndrome of the anterior part of the vermis remained obscure.

Edinger (16) distinguished anatomically between an older part of the cerebellum which he called the paleocerebellum (including the vermis and flocculus) and the neocerebellum (the hemisperes). Recent work (14) indicates that it is profitable to separate the flocculus, nodulus and associated parts which are closely related to the vestibular system. The remainder of the cerebellum, concerned with non-vestibular proprioceptive systems, is called by Larsell (25) the corpus cerebelli. It may in turn be subdivided into an older, paleocerebellar portion, and a newer, neocerebellar portion. Without any attempt to enter into a historical account of the development of our knowledge of the cerebellum, we may at once state briefly a conception of localization within the cerebellum which is confirmed even by modern electrical methods (15) and appears to clarify our ideas to the point of usefulness in the clinic. We shall later try to apply the conception to the localization of tumors.

These modern notions of cerebellar localization were clearly outlined by Fulton and Connor (21) in 1939, in recording the results of their experiments, and attempts have already been made to apply them to the clinic (Bailey (2), Bucy (9)). According to this scheme the cerebellum is divided functionally into three divisions: the archicerebellum, the paleocerebellum and the neocerebellum. These divisions with their connections may be schematized as follows in a general way, listing only those parts clearly belonging to each of the fundamental triad, many parts of doubtful or complicated connections being omitted.

	ARCHICEREBELLUM	PALEOCEREBELLUM	NEOCEREBELLUM
Cortical areas	Flocculus Nodulus	Culmen Lobulus centralis	Lobus ansiformis
Afferent connections	Vestibulocerebellar tracts	Spinocerebellar tracts	Cerebropontocerebellar tracts
Nuclei	Roof nuclei	Interpositum	Dentate
Efferent connections	Hook bundle Reticulospinal tract	Brachium conjunctivum Macrocellular red nucleus Rubrospinal tract	Brachium conjunctivum Microcellular red nucleus Lateroventral thalamus Areas 4 and 6 Pyramidal tract

The above named structures are not sharply differentiated either structurally or functionally but that they represent three functional systems is indicated by evidence from many sources. It is impossible to detail all this evidence here but a few examples may be given.

It is known that phylogenetically the cerebellum arises as a suprasegmental structure above the vestibular nuclei (22) and (if one excepts the octavolateral portion which disappears in higher vertebrates) has to do in the lowly aquatic vertebrates largely with equilibration. In this connection it is significant that those cyclostomes which swim freely have much larger cerebellums than do the parasitic forms which cling to a host (18). If we go to the other end of the vertebrate scale we find (32) that there is a tremendous development of the paraflocculus in those mammals which have returned to an aquatic habitat, such as the sealion, walrus, porpoise, manatte, etc. Also that in the sealion, which has forelimbs capable of a considerable degree of unilateral independence, the lobus ansiformis remains of carnivorous type, whereas in the walrus, which has mere flippers, useful only for swimming, this part of the cerebellum has lost its clear definition (31).

From such indications as the above came the hypotheses which finally led to fruitful experimentation. As examples we may mention first those of Bremer and Ley (6) on pigeons. This animal has very little in the way of cerebral cortex and no associated cerebellar hemispheres. But the vermis is well developed and it is possible to extirpate its anterior portion alone. The result is striking and consistent. There is a conspicuous release of postural mechanisms, the stretch reflexes are augmented, the positive supporting reactions are exaggerated and the pigeon assumes an attitude of strong extensor tonus with the head retracted. The dog and cat, after the removal of the cerebellum, have for a time intermittent seizures of opisthotonos and extensor rigidity. Removal of the cerebellum after decerebration causes a marked increase of the opisthotonoid position (29) and enhancement of the characteristic contraction of the anti-

gravity muscles. It has not been proven conclusively in the cat and dog that this opisthotonos is the result of a lesion of the anterior lobe, but it is likely since Sherrington showed long ago that electrical stimulation of the anterior lobe of the cerebellum diminishes the tonus of the antigravity muscles in the decerebrate animal. A similar effect is obtained by stimulation in the pigeon (Bremer). It is just to this region that the spinocerebellar tracts have their principal projection, also in mammals. This we may call the paleocerebellar system; it is old phylogenetically but not so old as the archicerebellar (flocculonodular) system since it did not develop until the vertebrates emerged onto land and became concerned with maintaining posture by means of limbs.

PALEOCEREBELLAR SYNDROME

Fulton and Connor (21) have been able to extend experimentation on this paleocerebellar system to the monkey. They found that ablation of the paleocerebellar anterior lobe (culmen and centralis, exclusive of lingula) causes in the monkey conspicuous disturbances in the postural sphere, increased tendon reflexes, pronounced lengthening and shortening reactions, and gross exaggeration of positive supporting reactions as well as a pronounced static tremor and incoordination of all four extremities. These observations have recently been confirmed and extended by Connor (10a).

Affections in which the anterior lobe of the human cerebellum is primarily affected are excessively rare. One of them is the primary atrophy described by Marie, Foix and Alajouanine (26) under the name of *atrophie paléocérébelleuse primitive* in which the atrophy of the Purkinje cells predominates in the lobulus centralis, culmen and declive. It is significant that they remark on the practical absence of nystagmus, the slight disturbance of speech, the relative integrity of the upper extremities, the slight asynergy of voluntary movement, the almost complete absence of hypotonicity, the trembling of the head and neck, and a certain degree of catalepsy. In noting the absence of pendular reflex they express their surprise since, as they remarked, it is rather constant in cerebellar lesions. The outstanding symptom was a gross disturbance of equilibration which made walking practically impossible; this dysequilibration persisted in the sitting position.

The catalepsy described by Babinski (1) in certain cerebellar cases is brought out as follows: The patient, lying on his back, flexes his lower extremities at knee and hip, and separates the feet; lifting the lower extremities from the bed. The limbs and the trunk at first oscillate from side to side but, after a few instants, the body and the inferior extremities become abnormally fixed. The significance of this finding is not clear, perhaps something in the nature of a lengthening reaction. At any rate the symptom has been described by Rossi, as well as by Marie, Foix and Alajouanine (26), in cases of primary paleocerebellar atrophy.

These studies indicate that the paleocerebellar system plays an important role in the maintenance and modification of the erect posture by means of the antigravity muscles of the neck, trunk and limbs. It follows that its influence on the trunk muscles is apt to be more important in man than in quadrupeds.

Now in the above clinical case the essentially paleocerebellar cortex was gravely injured. One would expect, then, to find increased tendon reflexes, lengthening and shortening reactions, exaggeration of the positive supporting reactions, static tremor and incoordination of the limbs. Fulton and Connor say nothing of any peculiar attitude in their animals resembling that of decerebellated birds. But Jackson called attention long ago to fits, in cases of cerebellar tumor, accompanied by retraction of the head and tonic extension of the limbs which resemble the attitude of decerebellated pigeons.

We may state at once that our patient had no such fits and did not lie in any posture of exaggerated extension of head, trunk or limbs. His head was usually turned to the left and he resented manipulation of his head and neck because it caused him pain. The tendon reflexes were increased but the presence of a Babinski sign on the left side, and possibly also on the right, would lead one to attribute the increase to involvement of the pyramidal tracts by pressure. No tremor was noted by any observer and incoordination of the limbs must have been slight since only one of five observers noted it. Positive supporting reactions were not looked for. Lengthening and shortening reactions were also not looked for; the only observation which could have any bearing on this point is the remark of one examiner that there was "abnormal resistance of the left upper and lower extremity to passive manipulation." However, in all probability this hypertonus was not a heightened supporting tonus.

In spite of the clearcut destruction of the paleocerebellar cortex in this patient, it must be admitted that there was observed nothing to suggest the symptoms resulting from destruction of this cortex in primates. Would it be possible to observe them if present in man? Increase of the tendon reflexes with a tendency to spread to synergic groups should be detected in any routine neurological examination. Static tremor, nodding and weaving of the head and trunk, and errors of range and direction in movements of the extremities should not be overlooked. Lengthening and shortening reactions and positive supporting reactions need to be looked for by special and unusual procedures. The plasticity of a muscle when passively manipulated is difficult to appreciate clinically and a recording apparatus, such as that devised by Schaltenbrand, is rarely at hand. As for the positive supporting reactions in the human being, they are rarely sought for. Schwab (33) demonstrated, however, that they may be present in cerebellar lesions and they should certainly be routinely sought for, by forcibly extending the wrist and fingers for the upper extremity and by forcibly dorsoflexing the foot and toes for the lower extremity. Until a systematic study is made of these reactions, however, in cerebellar lesions it is impossible to state that they will have any localizing value. Rademaker (30) states that he found positive and negative supporting reactions on the right side in a case of a tumor involving the anterior surface of the right cerebellar hemisphere. In a case with a tumor in a similar location Schwab (33) could not demonstrate them. But to our knowledge these reactions have not been systematically sought for in cerebellar cases.

The periodic fits described by Jackson as "cerebellar fits," which result from

acute increase of pressure in the posterior fossa caused by tumors, are characterized by symptoms of varied physiological significance. The loss of consciousness is doubtless due to acute compression of the aqueductal region; it is usually attributed to deafferentation of the cerebral cortex although there is no valid evidence that the presence of the cerebral cortex is essential to consciousness (27). The extensor attitude of the limbs is undoubtedly related to the syndrome of decerebrate rigidity (36) as described by Sherrington. When the rigidity is slight the tonic neck reflexes of Magnus-de Kleijn may be obtained (35) and the condition resembles the decorticate syndrome of the monkey (20). The disturbance of respiration is doubtless due to acute compression of the respiratory centers in the bulb. Finally the retraction of the head and dorsal curvature of the back which occurs in severe fits is doubtless due to superadding, on to the decerebrate attitude, release of the influence of the anterior lobe of the cerebellum as Sherrington pointed out long ago.

These manifestations give evidence of such widespread involvement of the central nervous system that "cerebellar fits" have little localizing value except to point vaguely and uncertainly toward the posterior fossa as the seat of the trouble. Nor is there any good reason to suppose that the opisthotonoid position would be produced in man by local destruction of the anterior lobe of the cerebellum. In the cat and dog such opisthotonoid fits occur sporadically for a few days following acute injury to the anterior lobe but soon disappear. In the monkey not even transitory fits occur (21) when the lesion is confined to the anterior lobe, so that in man one would not expect such fits to follow local destruction by tumor or other pathologic processes. It seems that, in order to provoke them in man, the injury to the cerebellum must be combined with injury to the brain stem.

Aside from the fact that symptoms of paleocerebellar origin become less and less conspicuous as the phylogenetic scale is ascended, one might suspect on purely anatomical grounds that they would be obscured in man since the magnocellular portion of the red nucleus and its efferent pathway, the rubrospinal tract, has become in man very unimportant (28, 34). Nevertheless, such signs as occur in lower animals should be systematically sought for, since in man the paleocerebellar portion of the vermis is not atrophic and may utilize other efferent pathways.

The syndrome of the flocculonodular system in man is now better understood. In children there arises from the region of the nodulus a malignant tumor, first clearly distinguished as a clinico-pathologic entity by Bailey and Cushing (4). This tumor, known as a medulloblastoma, causes a fairly consistent clinical syndrome which permits its recognition in most cases.

MEDULLOBLASTOMA OF THE POSTERIOR VERMIS

Case 2. A boy of 5 years was referred by Dr. M. C. Shell of Chicago. He was admitted on May 13, 1940 to the Pediatric Service of Dr. Julius Hess.

He was said to have been entirely well until 3 weeks before admission to the hospital, when he began to vomit in the morning on getting out of bed. He had no other complaints

at the time and seemed well during the rest of the day. About a week before he began to complain of headache; he staggered when walking, and vomited repeatedly.

On admission the child was cooperative. He walked on a broad base, with markedly unsteady gait. His head was not noticeably enlarged and Macewen's sign was absent. His neck was somewhat stiff and he did not like to have it flexed. The optic discs were swollen about 1 diopter. Dysmetria of the hands was slight. Nystagmus also was inconspicuous, more marked to the left. Since a history was obtained of playing with red lead, his blood was examined and found to contain a normal amount of lead. X-ray photographs of the head showed no dilatation of the sutures; those of the wrist showed no lead lines (10).

A diagnosis of midline cerebellar tumor was made, probably medulloblastoma.

On May 22, a suboccipital exploration was made which disclosed a tumor which had already spread into the leptomeninges. Since extirpation was impossible, a decompression was left. Roentgen radiation was begun, but on June 2 he began to have generalized convulsions, his temperature rose to over 106°F. and he died on June 18, 1940.

FIG. 2. Case 2. Tumor (medulloblastoma) destroying the nodulus and part of the pyramis

Necropsy was limited to the examination of the central nervous system. The brain and spinal cord appeared grossly to be covered with a whitish exudate. The third and lateral ventricles were dilated slightly. On medial sagittal section of the brain there was found a tumor (fig. 2) 3.5 x 2 cm. in diameter, developing from the region of the nodulus and extending into the cavity of the fourth ventricle. It had destroyed the nodulus and the inferior half of the pyramis and pushed the rest of the vermis upward and forward. Among the roots of the cauda equina were large nodules of tumor.

The tumor was composed of cells with scanty cytoplasm and large oval nuclei with abundant chromatin. Mitoses were numerous. There was no intervascular necrosis (the gross appearance of central necrosis visible in the photograph is due to post-mortem disintegration) and no connective tissue apart from the blood vessels. The tumor invaded the leptomeninges and spread down the spinal subarachnoid spaces to the cauda equina, forming large masses of tumor among its roots. It had destroyed the nodulus and part of the pyramis but, contrary to the sarcoma of the first case, its margin against the cerebellar tissue was fairly sharp with no tendency to invade along the blood vessels. This tumor was a typical medulloblastoma.

ARCHICEREBELLAR SYNDROME

The characteristics of the syndrome in this case are gross disturbance of equilibration in the erect posture with inconspicuous incoordination of voluntary movements of the limbs, especially of the hands, and relative absence of nystagmus. This syndrome is accurately reproduced in monkeys by extirpation of the flocculus and nodulus. "The studies of Robert Dow (1936, 1937, 1938) in cats, monkeys and a chimpanzee indicate that ablation of the flocculonodular lobe causes disturbances of equilibrium identical with those seen in midline cerebellar tumors of children (especially the medulloblastomas), i.e., swaying, progression on a broad base and so-called "trunk ataxia"; individual movements of the extremities, however, are not affected and there are no changes in tendon-reflexes or in postural resistance of the extremities (21)."

This syndrome was described in such cases by Bailey (2), called the syndrome of the vermis cerebelli and erroneously ascribed to a lesion of the paleocerebellum. The work of Dow leaves no doubt that it is an archicerebellar syndrome, or a syndrome of the flocculonodular lobe.

NEOCEREBELLAR SYNDROME

The syndrome of the neocerebellum (Brouwer) has been magisterially exposed by Gordon Holmes (23) on the basis of war wounds. The presenting symptoms are homolateral 1) hypotonia, 2) irregularity of movement, principally of volitional movement, 3) errors of range, rate and direction of movement, generally spoken of as asynergy, and 4) tremor. There is a nystagmus provoked on lateral deviation of the eyes which is coarser and slower on looking to the side of the injury to the cerebellum. Tremor also is not a prominent symptom unless the deep efferent nuclei are involved.

There has been a great deal of discussion as to whether hypotonicity is an essential part of the syndrome, since it is not a prominent feature of the symptoms following extirpation of the cerebellum in other animals, even the monkey. But recently Botterell and Fulton (5) have shown that ablation of the cerebellar hemisphere in the chimpanzee gives rise to a permanent and definite homolateral hypotonicity. Only the nystagmus which accompanies such a lesion in man has not yet been produced in other animals, even the chimpanzee. This syndrome is often produced by tumors of the cerebellum in children. Such a tumor may be illustrated here.

ASTROCYTOMA OF THE CEREBELLAR HEMISPHERE

Case 3. The patient was a girl of 10 years referred by Dr. C. Klontz of McHenry, Illinois. She was admitted on September 14, 1940. She was said to have been perfectly well until May, 1940, when she began to complain of headache upon awakening in the morning. In June she began to vomit her breakfast. About the same time she began to see double. In July she complained of dizziness and would complain of pain if her neck were turned. Her gait became very unsteady in the last two months, and she veered constantly to the left.

The child was slender, cooperative. The head was held stiffly and tilted to the left. The head was not noticeably large. The optic discs were swollen 6 diopters. There was a right rectus palsy. The gait was very unsteady with deviation to the left. There was asynergy and hypotonicity of the extremities, more on the left side. X-ray photograph of

the head showed marked convolutional markings and separated sutures. Marked nystagmus on looking to the right and left was observed.

The child was thought to have a cerebellar tumor, probably an astrocytoma mainly in the left hemisphere, and an operation was planned. Early in the morning of September 18 she was given an enema. Straining to expel it provoked an attack of severe headache; she became comatose, with retracted head, and died promptly of respiratory failure.

Necropsy, confined to the head, disclosed a tumor (fig. 3) of the left cerebellar hemisphere, extending into the vermis but scarcely into the right hemisphere. It was whitish, firm, sharply circumscribed from the cerebellar tissue. The central portion of the tumor was occupied by a large cystic cavity filled by a gelatinous mass which had doubtless been fluid but was coagulated by the fixative.

Microscopically the tumor was composed of astrocytes; blood vessels were rare, and the margin of the tumor against the cerebellar tissue was sharp. It had not invaded the subarachnoid spaces. This tumor was a typical astrocytoma.

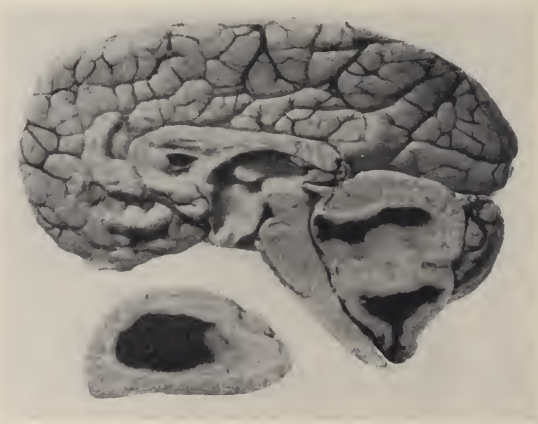

Fig. 3. Case 3. Tumor (cystic astrocytoma) of the left cerebellar hemisphere and involving also the vermis

The tumor involved the vermis but lay primarily in the left hemisphere and this location was translated clinically in the predominance of hypotonicity and incoordination in the left limbs, deviation to the left in walking, tilting of the head to the left and nystagmus, coarser and slower on looking to the left. Astrocytomas often arise in a cerebellar hemisphere; medulloblastomas, almost never.

CONCLUSIONS

1. The syndrome of the ansiform lobe is frequently produced in children by astrocytomas. It is characterized by homolateral hypotonicity, asynergy and asthenia of the homolateral extremities and by nystagmus, coarser and slower when the eyes are turned to the side of the affected lobe.

2. The syndrome of the flocculonodular lobe is often caused by cerebellar tumors during childhood, usually by medulloblastomas but also by astrocytomas which develop in the posterior vermis. It is characterized by a gross disturbance of equilibration, making walking very difficult, whereas there is very little asynergy on voluntary motion of the extremities while the patient is lying on the back. Moreover, nystagmus is inconspicuous or absent.

3. The syndrome of the anterior lobe has not been clearly distinguished in man. But the opisthotonoid position assumed in "cerebellar" fits may be due in part to acute suppression of its influence. This sign has little localizing value in case of tumor since it is observed only in association with widespread disturbance of the function of other structures in the posterior fossa. Of the other signs which follow destruction of the anterior lobe in the monkey only the positive supporting reactions have been observed in man. It would seem advisable to search routinely for these reactions in every case of cerebellar tumor, possibly also for Babinski's catalepsy. Tumors involving the anterior lobe primarily are rare and of unusual structure.

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ACUTE GENERALIZED ATAXIA OF ENCEPHALITIC ORIGIN: DISCUSSION OF LOCALIZATION OF LESIONS

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Knowledge of acute generalized ataxia is gradually being increased but instances of the type here reported are so uncommon that the publication of observations of single cases would seem to be justifiable.

CASE REPORT

History. The patient, Louise J., a colored hospital maid, 19 years of age, single, was admitted to the Medical Service of the Johns Hopkins Hospital complaining of headaches, staggering gait, thickening of speech, and inability to use her hands for buttoning her clothes or for bringing food to her mouth.

Three weeks before admission to the ward she had begun to have headaches in the front and sides of the head; these gradually increased in severity and the discomfort extended backward to the occipital region. She described these headaches as being "pounding and aching" in character. They were not accompanied by nausea, vomiting or fever and they were not relieved by aspirin. After two weeks of these headaches she began to feel weak and dizzy and went to bed. On trying to get up next day she found that she was extremely weak and on attempting to walk found that she staggered and had "difficulty in managing her feet." The headaches were worse than before. She went back to bed. On the following day she noticed that her speech was thick and that she was unable to button her clothes. On the third day before admission, the movements of her upper extremities had become so disturbed that she was unable to feed herself and the movements of the lower extremities had become so weak and uncertain that she was unable to walk at all. As the symptoms persisted she was admitted to the hospital ward for study and treatment.

Except for an occasional cold, the patient said that she had always been well. No history of gonorrhoea or syphilis could be elicited. The patient had never manifested any neurological symptoms before. The family history threw no light on the case. No other member of the family has had ataxia.

Examination. (Dr. F. T. Billings). The temperature was 99°F.; the pulse rate, 70; the respiratory rate, 20; and the blood pressure, 110 systolic, and 90 diastolic. The patient was well developed and well nourished. She was intelligent and cooperative and did not look ill as she lay quietly and comfortably flat on her back. The headaches ceased on admission. The speech was hesitant, thick, slurred, and somewhat nasal in quality. The mental state was clear. There were no significant abnormalities of the skin or of the skeleton. No enlarged lymph glands could be found.

The eyes were normal. The pupils were equal and reacted to light and on accommodation. The extraocular movements were normal and there was no nystagmus. The visual fields were intact in outline. On ophthalmoscopic examination the eye-grounds were quite normal and there was no dilatation of the retinal vessels.

The nose, ears and mouth were normal. The teeth were in good repair. The slightly coated tongue could be protruded in the midline without tremor. The tonsils were small and the pharynx appeared normal. The thyroid gland was not enlarged nor was it nodular. There was slight dysarthria.

The thorax was of normal form and the breasts on examination were negative. The respiratory movements were normal and the lungs and pleurae were negative on palpation, percussion and auscultation.

The heart was of normal size and the apex beat was visible and palpable in the fifth left

intercostal space medial from the mid-clavicular line. The heart beat was regular and the heart sounds were normal. The aortic second and the pulmonic second sounds were approximately equal in intensity. The pulses at the two wrists were equal and of good volume. No thickening of the peripheral arteries could be detected. There was no cyanosis and no edema.

The abdomen was symmetrical, soft and free from tenderness on palpation. No hernia existed and no tumor masses could be felt. The liver and spleen were not enlarged and the kidneys could not be felt.

On *neurological* examination no abnormalities of the special senses or of cutaneous sensibility could be elicited. The actual strength of muscular contractions was not impaired, nor was there any marked change in muscular tonus. The patient could walk, but very unsteadily (staggering gait) and the right arm failed to swing on walking (loss of associated movement). On standing there was some tremor of the whole body. There was marked incoordination of the movements of the upper extremities; the patient could not feed herself and could not button or unbutton clothing. The heel-knee-shin test was performed poorly on both sides, worse on the right than on the left. There was bilateral adiadochokinesis, more marked on the left than on the right. The patient was right-handed. The Romberg sign was positive; the Kernig sign was negative, as was the Babinski sign. The superficial and deep reflexes were active and equal on the two sides. There were no sphincter disturbances.

Laboratory Data. Blood: Red blood cells, 4,780,000; hemoglobin, 99 per cent; white blood cells, 10,840 with normal differential count; Wassermann reaction, negative. Urine, negative. Cerebrospinal fluid: Pressure, normal; cell count, 250 per cu. mm. (87 per cent lymphocytes and 13 per cent polymorphonuclear leucocytes); Pandy test, positive; colloidal mastic curve, low; Wassermann reaction, negative; no bacteria present.

Course. Improvement was rather rapid. The headaches and dizziness disappeared promptly. After two days the speech had markedly improved and the ataxia became much less marked, although the gait was still unsteady and some incoordination of movements of the extremities persisted. She was able to feed herself with her left hand. Within one week the ataxic symptoms had largely subsided and the cell count in the cerebrospinal fluid fell to 100 (98 per cent lymphocytes). The complement fixation test for lymphocytic choriomeningitis was found to be negative (Dr. Turner).

COMMENT

Localization of the Neurological Lesions: The acutely developing generalized ataxia (with admixture of static and dynamic ataxia) pointed very definitely to either the cerebellum itself or the extra-cerebellar conduction paths. If the process were localized in the cerebellum itself it would have to be widespread since not only the vermis but the cerebellar hemisphere would necessarily have been involved. Against such widespread cerebellar involvement two points may be urged: viz., the absence of hypotonia of the muscles and the ataxia of the speech muscles (dysarthria).

In the literature two groups of cases of acute generalized ataxia have been reported:

(1) Cases with cerebellar localization (Nonne, Bechterew, Schnitzer).

(2) Cases with localization in the subthalamic region (Leyden, Westphal, Margulies).

The symptoms presented by the patient reported here correspond to those encountered in the second group. The lesions (largely transient) must have been in the tegmental region of the cerebral peduncle on both sides, involving

the extra-cerebellar pathways there (cf. Margulies, M. S., Akute allgemeine Ataxie, Ztschr. f. d. ges. Neurol, u. Psychiat. 90: 104, 1924).

That there was some meningeal irritation was shown by the findings in the cerebrospinal fluid.

Nature of the Neurological Lesions: The acute onset with slight elevation of temperature is strongly suggestive of an inflammatory process as is the transient nature of the symptoms and the findings in the cerebrospinal fluid. It is almost certain that the entire clinical picture was the result of an acute epidemic (v. Economo) encephalitis.

TETANY OF THE NEW BORN: A REVIEW

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A decade ago it was very difficult to convince pediatricians that tetany could occur in the new born infant, in fact there were definite statements in pediatric textbooks that it was never seen at this early age. In spite of these categorical statements a few cases appeared in the literature which seemed to show typical tetany in the new born. Kehrer (1) in Switzerland in 1913 was the first to call attention to the disease and Shannon (2, 3) in the United States insisted on its importance. Definite cases had also been reported, one by Powers (4) and one by Griffith (5). In 1931 Bass and Karelitz (6) described three new born infants with hyperpyrexia and convulsions, a syndrome which they ascribed to tetany as the symptoms were abruptly cured by calcium gluconate. These cases and those described by Shannon seemed to stimulate interest in the subject and called pediatricians' attention to the fact that this condition really existed. Papers on the subject began to appear and soon a large number of cases were reported (7, 9, 10, 11, 12, 13, 18, 20, 26). Rothstein (21) in New York City reported a number of cases giving an accurate description of the symptomatology and treatment. Together with Hellman (20) in 1935 he called the attention of obstetricians to the disease, a very important step since many cases must have escaped notice as obstetricians were not aware of the existence of the condition. That the disease is not only a real one but is not uncommon is shown by the report of Graham (18) before the International Congress of Pediatrics in 1933. He described twenty-three cases of convulsions in infants under four months of age all of whom had hypocalcemia. In 1936 Farr (23) reported three cases and collected sixty-four cases from the literature exclusive of the twenty-three cases just mentioned. It is thus evident that the disease is not at all rare.

SYMPTOMATOLOGY

The symptomatology of tetany in the new born is of interest because the illness may appear in several quite dissimilar forms. It is perhaps on account of its protean manifestations that it has frequently been overlooked and that many cases have surely gone undiagnosed, some of them recovering, others dying in the belief that they were cases of birth injury.

The most common clinical picture is that in which, as one might presuppose, the central nervous system is chiefly involved. An infant soon after birth or within the first fortnight of life appears irritable, cries a good deal, starts at noises and then begins to twitch. Following this convulsions make their appearance. They may be tonic or clonic and may recur every few minutes or be isolated in their occurrence. All other symptoms characteristic of infantile tetany, such as Chvostek's sign, carpo-pedal spasm, Trousseau's sign may be present or absent. The convulsions may be generalized or may appear to

involve one side of the body or one extremity more than the rest. Convulsions may be the only sign of the disease as in the case reported by Walker (22). Fever may be present. The following is an excellent example of a case of this type.

CASE REPORT[1]

History. A. L. was born at term on July 15, 1940. He was the first child of healthy parents. The pregnancy was normal. The baby was delivered by low forceps and there was no evidence of injury. He was bottle-fed and returned from the hospital at the age of two weeks. On the following day the nurse noted convulsive seizures coming on very frequently. The child was again hospitalized. Tetany was suspected and blood chemical studies were ordered.

Examination. The infant did not appear toxic. Physical examination was negative except for the presence of generalized convulsions lasting one to two minutes and occurring every five minutes. They were clonic in type and affected the entire body. The fontanelle was flat. There was no neck rigidity. The heart and lungs were normal. The abdominal examination was negative except for a slight oozing from the umbilicus. The ears, eyes, nose and throat were normal. The skin was clear. The temperature was 99°F. Radiograph of the chest was negative. Lumbar puncture was unsuccessful. Blood count showed a leucocytosis (16,450 white blood cells) with a normal differential count. Blood calcium was 8.5 mg. per cent, blood phosphorus 8.8 mg. per cent.

Course. The child was given 1.0 gm. calcium chloride by mouth and sodium phenobarbital, gr. ½, by hypodermic injection.

The convulsions decreased in frequency and subsided completely within two days. The infant took its feedings well, and five days after admission to the hospital the calcium in the blood had risen to 10.5 mg. per cent. He was discharged August 5 in excellent condition, still taking 3.0 grams of calcium chloride daily. He remained well and had no further symptoms.

A second group of cases are those described by Bass and Karelitz (6) in 1931 under the title of "Tetany Accompanied by Hyperpyrexia and Vomiting in the First Days of Life." Three cases were described characterized by infants who became extremely ill in the first days of life. They vomited frequently, their abdomens became markedly distended; the temperature rose to a great height. Two of the children had marked dysphagia. They showed signs of nervous irritability, their cry was hoarse, Chvostek's sign was very marked, they exhibited carpo-pedal spasm and finally convulsions. In one case cardiospasm was pronounced and was proven by barium and radiography.

Infants with this syndrome give the impression of suffering from intestinal obstruction. The constipation, the constant vomiting and above all the greatly distended abdomen all point toward that diagnosis. One such case that I was called on to see was in violent convulsions with a temperature of 105°F. The physician and obstetrician were seriously considering an exploratory laparotomy. Because of the similarity of the clinical picture to the variety of tetany we are discussing, an intravenous injection of calcium gluconate was given at once. The result was most dramatic, the infant relaxed, the convul-

[1] Reported through the courtesy of Dr. Herman Schwarz.

sions and vomiting ceased, the temperature gradually came down and the child went on to complete recovery.

The third group of tetany cases is that in which edema is a prominent factor. In the original paper of Kehrer several cases are described which among other symptoms showed a brawny edema of the abdomen and chest. Shannon also emphasized the presence of edema. One must not overlook the fact that edema in the new born may be a symptom of tetany. It must also be remembered that low calcium may be present in these cases without any other symptoms of tetany. I was shown such a case by Dr. J. L. Rothstein, who later published its history (21). This infant had fever, vomited continuously and had a persistent colicky cry on the first day of life. A brawny edema was present about the vulva. When thirty-six hours old, tetany was suspected and a calcium estimation of the blood revealed 7.0 mg. per cent. Calcium was given with prompt recovery. In this infant there were no neurologic symptoms whatever.

Symptoms of any of these three types may appear together, thus there are cases with high fever and convulsions, or cases with edema and vomiting, or some with edema and convulsions. As has been pointed out by Shannon, edema, the expression of some underlying metabolic disturbance, may involve the subcutaneous tissues giving rise to visible swelling or may be limited to the brain causing the more recognizable neurologic disturbances.

As was mentioned above one must not expect any or all of the typical symptoms of infantile tetany to be present. In some of the cases Chvostek's sign may be extremely active. In one infant described by Bass and Karelitz tapping on the cheek threw the whole child into spasm. However, one must not absolutely rely on the presence of this sign as a diagnostic aid, especially when it is not very pronounced, for Mitchell and Stevenson (8) pointed out that it is often present in the new born without any symptoms of tetany. Out of fifty-five new born infants investigated who showed a positive Chvostek's sign, fifty had blood calcium of between 10 and 12 mg. per cent. Trousseau's sign has been described and in several instances electrical reactions have shown the typical tetany reaction.

PATHOGENESIS

It is natural that a symptom complex as varied as this one should arouse much interest as to its etiology. It was evident early in its study that this form of tetany differed considerably from the tetany of older infants. As we have seen, the signs so characteristic of the disease in older children, such as Trousseau's and Chvostek's signs, laryngospasm and changes in electrical irritability of nerves, may be absent. The illness is not seasonal nor is it connected with rickets. It is seen more often in private than in ward patients. It has not been described as occurring in colored infants.

In 1933 Cohen (11) reported three cases and after discussing the condition concluded, "Tetany occurring in very young premature infants may be the primary expression of a low calcium form of rickets, and may not be suprarachitic as in older children. Tetany in very young immature infants with no

clinical or x-ray evidence of rickets but with evidence of osteoporosis may possibly be a non-rachitic form of tetany. A congenital deficiency in calcium may develop into the type of infantile tetany comparable to that resulting from osteomalacia and celiac disease."

In the same year Bloxsom and Nicholas (12) suggested that there might be a substance in the blood of the infant preventing ionization of the diffusible calcium, which substance might be formed in the placenta.

Maslow (13) also in 1933 reported five cases with careful blood chemical studies and an interesting discussion in which he comments on the low calcium and the high figures for blood phosphorus and suggests that the parathyroid glands may be at fault.

Meanwhile Shannon (14, 16, 28) stressed the possibility of alkalosis due to anoxemia in the new born as a factor in the causation of the symptom.

The role of the parathyroid is again mentioned by Gorter and de Does (17) who even show a section of the gland which is partly replaced by tissue resembling thymus.

Farr (23) in 1936 in reporting three cases calls attention to the fact that in tetany of the new born recovery with treatment is immediate whereas in ordinary tetany to obtain a cure, treatment must be carried on over a long period of time. He states, "the disease behaves as an endogenous chemical disturbance which is usually not fatal," and again stresses the absence of any connection with rickets as shown by the age of the infant, the absence of radiographic evidence, absence of clinical signs of rickets and the rapidity of the cure. This author also inclines toward parathyroid disturbance as the underlying cause of the disease.

The most thorough piece of work on the etiology has been done by Bakwin (29), who in 1937 reported four cases in new born infants all with low calcium. He examined a series of normal new born infants and showed that there is a tendency for the blood calcium to fall during the first four days of life. This he believes may be due to a disturbance of the parathyroid glands which apparently have not yet taken on their complete function. He points out that hypocalcemic tetany occurs as the result of 1) parathyroidectomy; 2) after ingestion or injection of phosphate; 3) after deprivation of sun light or vitamin D; 4) during disease of the upper intestinal tract such as celiac disease, sprue or chronic pancreatitis. The disturbance in the calcium phosphorus ratio is moreover accentuated first by the abrupt neonatal drop in calcium, and second by the small amount of phosphorus excreted in the infants urine. A contributing factor is the endogenous release of phosphate due to starvation in the first few days of life. Fever which increases the break down of tissue also favors tetany through the endogenous release of phosphate. (This would explain why in several of the reported cases (14, 15, 21), tetany has appeared when febrile illnesses, such as pneumonia or otitis attacked the new born). The fact that most of the cases of tetany in the new born are infants fed on cows milk is also important, since its phosphate content is so much higher than that of breast milk.

Denzer, Reiner and Weiner (31) in 1939 corroborated the neonatal drop in

calcium. Although they showed that the phosphorus is higher in the neonatal blood than in the cord blood, it follows no definite constant curve. They do not believe that available data justify the conclusion that the parathyroids are at fault although they agree that the hypothesis is a likely one.

The consensus of opinion therefore is that tetany of the new born is a hypocalcemic form of tetany the result of a disturbance in the calcium and phosphorus metabolism probably due to temporary disturbance of the parathyroid gland.

DIAGNOSIS

Tetany must be included among the diagnostic possibilities in all cases of convulsions in the new born. There is nothing characteristic about tetany convulsions. They may be local or general, unilateral or bilateral, frequently repeated or isolated. Guild (10) stresses the fact that infants with tetany of the new born appear to be normal between the convulsive attacks. As was mentioned above one must not expect to find all the characteristic signs of tetany as it appears in older children; in fact the disease may be present without the manifestation of any symptoms referable to the nervous system.

If suspected, the diagnosis can be settled by blood determinations of calcium. The amount of calcium in the blood of normal new born infants has been determined and found to be 11.0 mg. per cent with a standard deviation of 0.92 mg. per cent (Bakwin and Bakwin). When this is diminished the symptoms we have described may appear. In rare instances hypocalcemia may be present in apparently normal infants. In a routine examination of fifty-five normal newborns Mitchell and Stevenson (8) found the blood calcium to be 7.3 mg. per cent in one case and between 8 and 10 mg. per cent in four cases, the remainder being between 10 and 12 mg. per cent. Such cases of hypocalcemia may be considered cases of potential tetany.

In many instances cases have been reported as tetany of the new born where calcium determinations have not been done. This has led to much confusion because of the resemblance between tetany of the new born and cerebral birth injury. However, I believe the rapid response of the symptoms to calcium medication is so characteristic that the therapeutic test may be used as a diagnostic aid.

The electrical reactions are difficult to obtain in very young infants, but are reported in some of the cases as typical of tetany (27). In some cases in spite of very low blood calcium figures electrical reactions have been normal (23).

TREATMENT

Since the essential factor in the causation of tetany of the new born is the low blood calcium, the most important therapeutic measure is the administration of calcium itself. This may be given by mouth, by intramuscular injection or by intravenous injection. Where symptoms are severe, the intravenous route is advisable. Calcium gluconate is easily procurable and may be given in doses of 5 to 10 cc. After this, calcium should be prescribed by mouth. The best preparation is probably calcium chloride because it contains considerably more calcium (30 per cent) than does the gluconate (9 per cent),

besides which the chloride ion is much more powerful than the gluconate, its acidity being an important factor. It is true that calcium gluconate is not as irritating to the stomach as is the chloride and many cases of tetany have been cured by its use. Occasionally, however, it is not powerful enough as indicated in an instructive case described by Walker (22): A normally born infant began to have spontaneous twitching of the face and arms. Blood calcium was 5.5 mg. per cent. The child was given 0.6 gm. calcium gluconate daily with "occasional intramuscular injections of 0.5 to 1.0 gm. calcium gluconate." The convulsions continued and on the eighteenth day the infant was admitted to the New Haven Hospital where the blood calcium was still found to be only 5.3 mg. per cent. Therefore, 3.3 grams of calcium chloride were given by gavage and repeated on account of vomiting. Next day 2 gms. were given in the milk mixture. No convulsions occurred after the gavage. The blood calcium had risen to 9.7 mg. per cent on the twenty-second day of life.

It is important as emphasized by numerous authors (13, 14, 16) that calcium medication be continued over several weeks because it often takes considerable time before the blood calcium returns to normal.

To enhance the effect of the calcium some authors give ammonium chloride (12). There is no question that the increase of acidity by the use of the chloride ion is valuable, but I would warn against its use without careful control. I have seen one infant die from acidosis due to receiving calcium chloride over too long a period.

The intramuscular injection of calcium is a simple method of its administration, especially when compared with the intravenous route which is often technically so difficult in the new born infant. However, there is a real danger of induration and abscess formation at the site of injection which may lead to severe consequences. Even the very newest preparations of calcium gluconate, specially prepared to be non-irritating, may give rise to local abscess. Unless absolutely necessary, therefore, calcium injections into the muscles should be avoided. In this connection Shannon (28) has reported an interesting phenomenon. He described deposits of calcium in the lung (proven by radiography) and in arteries adjacent to the site of injection. These deposits gradually disappeared, but must be considered an unpleasant complication.

Vitamin D in the form of haliver oil, oleum percomorphum, Drisdol or any other concentrates should be prescribed in large doses. Bakwin used forty drops of Viosterol daily.

An interesting result with Dihydrotachysterol was recently reported by Bloxsom (34). A three week old infant who had been getting vitamin D, showed nervousness and twitching with a blood calcium of 5.4 mg. per cent. The infant was given 12 gm. calcium gluconate daily in milk. Five days later the calcium was still only 4.7 mg. per cent. A. T. 10 was given in doses of five drops three times daily. This had to be increased to fifteen drops before there was any result. After four days the calcium rose to 11.4 mg. per cent, but symptoms returned when the drug was reduced to ten drops, necessitating return for a time to the larger dose. The infant was cured.

The calcium in this case was not only followed by blood studies but also in

the urine by the use of Sulkowitch's reagent (29). Calcium is normally demonstrable in the urine by this simple test since the normal level of blood calcium is above the threshold for the excretion of calcium in the urine. This threshold varies between 7.5 and 9.0 mg. per cent. If there is no precipitate with the Sulkowitch reagent, the blood calcium is probably from 5 to 7.5 mg. per cent. If therefore one suspects tetany one can make a rough estimation of the blood calcium by simple addition of Sulkowitch's reagent to the urine. If there is no precipitate one can be sure of a very low blood calcium. This should prove a rapid "bed side" test.

The value of parathormone is still disputed in tetany of the new born. Bakwin does not believe it necessary. Shannon (28) among others advocates its use. There are numerous cases reported in which the cure seems to have been accelerated by parathormone injections (1, 27). It would seem that in cases where there is delay in the return of the blood calcium to normal, an injection of parathormone is indicated.

SUMMARY OF THE TREATMENT

If the condition of the infant is serious, i.e., if convulsions, twitching or hyperpyrexia are present, ½ ampoule of calcium gluconate (10 per cent) should be injected intravenously. If the convulsions do not respond to this, sedatives such as chloral by rectum or sodium phenobarbital should be given. The calcium injections may be repeated several times at four to six hour intervals if necessary. Calcium chloride should be administered by mouth in doses of 1.0 gm. every four hours either in milk or by gavage. This oral medication should be continued until the infant is symptom-free when the frequency of the dose may be diminished. It should not be discontinued until the blood calcium has returned to normal. If the administration of calcium fails to bring about relief, an injection of parathormone should be given. It is well to give vitamin D at the same time as the calcium, in order to promote better absorption.

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SKIN REACTIONS. XIV

The Effect of Atropine on the Mecholyl and Whealing Reactions of the Skin[1]

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INTRODUCTION

Although many experiments have been performed to ascertain the nature of the mechanism responsible for the whealing response to heat, cold, and light, these investigations have by no means given explicit information about the substances producing the phenomenon involved. According to Grant, Pearson, and Comeau (1), certain types of urticaria provoked by physical stimuli like heat and cold are apparently dependent upon the liberation of acetylcholine or substances very closely related to acetylcholine in their pharmacological effect. More recent work of Hopkins, Kesten and Hazel (2) also shows that a whealing response in the skin occurs when acetylcholine is introduced into the skin by electrophoresis or when injected. They inferred that in patients with heat urticaria, the liberated acetylcholine produces whealing in the skin. The similarity of this type of reaction to the normal whealing reaction to histamine led Grant and his associates to conclude that in the types of vasomotor reactions under discussion, the liberation of acetylcholine or the injection of acetylcholine produces secondary release of a histamine-like substance from the cutaneous cells which in turn produces whealing.

Skin reactions of the type under discussion can be readily investigated by the method of electrophoresis. Not only is histamine readily introduced electrophoretically but also epinephrine, atropine, and many other substances are transported into large areas of relatively uninjured skin. In this way skin reactions may be investigated with a minimum of skin damage. The study of pharmacologic antagonism by this method is especially simple because the blocking effect of a substance like atropine on the vasodilating properties of Mecholyl can be directly investigated. In this communication certain studies of the antagonism between atropine and Mecholyl are reported in addition to the effect of atropine on the flare of the wheal and on the nature of the response in a special type of vasomotor hypersensitiveness found in Urticaria solare. Mecholyl was selected in preference to acetylcholine because the latter is unstable in the presence of tissues which contain cholinesterase.

METHODS

In performing electrophoresis experiments of the type to be presented, it is important to have the solutions diluted with distilled water rather than with

[1] This investigation has been aided by a grant from the Josiah Macy, Jr., Foundation.

physiological saline because the salt carries the current (3). The acetylcholine-like substance used in our experiments was a preparation of Mecholyl (Merck). Solutions of atropine sulfate were employed. At the dilutions used, there usually were not enough hydrogen ions present to account for the irritation or reaction of the skin. An ordinary electrophoresis apparatus with suitable current densities which are given with each experiment was the source of current. Material in solution was applied to canton flannel and applied to the skin with an aluminum foil electrode as the metal electrode. In addition, a few experiments were done with the stable choline compound, Doryl, (carbamino choline hydrochloride) with no change in results.

In studying the effects of these pharmacologically active substances on the blood vessels of the skin, usually a rectangular, square, or triangular shaped piece of canton flannel saturated with a solution of the material was applied to the skin. This area was mapped out and an antagonistic effect was subsequently studied close to and over the same area. The exact procedure is described in more detail subsequently.

EXPERIMENTAL

The electrophoresis of atropine. Depending on the current density, the individual employed, and the concentration of the atropine sulfate, the reaction of the skin to the electrophoresis of atropine varies (4). Thus, with dilute solutions of atropine, (e.g., 1:1000) papules form presumably around the pores of the skin. These small papules would correspond roughly to those formed from about 1:1,000,000 histamine given electrophoretically. The following is a typical experiment illustrating the reaction to atropine. Subject: H. A. A. 1:1000 atropine sulfate administered for five minutes with a current of 0.5 ma. Many small scattered papules were observed but no flare. After about forty minutes, the papules disappeared. The skin regained its normal appearance after about 1 hour. The disappearance of the papules and the reappearance of the normal color of the skin is a convenient sequence for experiments of this type. Although it was found that the whealing and reddening of the skin to the electrophoresis of atropine with higher current densities interfered with subsequent experiments on the inhibition of Mecholyl by atropine, after an hour following the electrophoresis of the atropine itself, the effects of Mecholyl were readily observed.

In the experiment just cited it should be noted that atropine produced a wheal but no flare. On the other hand, if stronger current densities were used or a higher concentration of atropine was employed, a fairly transient flare appeared. The following experiment illustrates this.

Subject: G. N. 1:1000 atropine sulfate, current density: 0.2 ma. This produced a semiconfluent wheal with a slight flare. Similar results were obtained with current densities of 0.12 ma.

It is of some interest that atropine itself which is known to inhibit acetylcholine-like actions produces a whealing response. In addition, the atropine does not prevent the appearance of a flare to the whealing response of atropine

itself. This point will be discussed subsequently when the experiments dealing with the effect of atropine on the vasodilatation produced by Mecholyl and by light are presented.

The inhibition of the Mecholyl vasodilatation by atropine. It is well known that atropine blocks the vasodilator muscarine-like effects of acetylcholine, Mecholyl (acetyl-β-methyl choline), doryl (carbaminocholine) and of some of the other choline compounds.

It was at first important to choose subjects who were not irritated to too great an extent by either the atropine or the electric current even though somewhat small current densities were applied. However, with the improvement of our technic and with our understanding of the typical response of the skin to the electrophoresis of atropine, it was possible to get reproducible results.

As has been shown previously, the skin acts as a reservoir for certain pharmacologically active substances. Thus, if histamine is introduced by electrophoresis into the skin, a comparatively large quantity of it remains in the skin, the skin acting as a depot for the material for days (5). Similar reservoir effects have been observed for epinephrine (6). It was anticipated, therefore, that if a suitable period elapsed, atropine introduced by electrophoresis would not be rapidly absorbed but would remain in the skin even though the whealing response and the irritation had disappeared. For this reason, and it has subsequently been found experimentally, studies on the inhibition of the Mecholyl reaction by atropine were conveniently performed about one hour after the atropine had been introduced by electrophoresis. On the other hand, inhibition effects and blanching of mecholyl flush by atropine was also observed after the Mecholyl had been introduced in the skin of a suitable subject. That is, under proper conditions, either the Mecholyl may be given first to show the inhibition effect or the atropine may be given first.

The following is a typical example of an experiment illustrating the inhibition of Mecholyl by a skin treated with atropine.

Subject: H. A. A. Time: 10:30 A.M. 1:1000 atropine sulfate administered electrophoretically. Area of electrode: 10 sq. cm. Current: 0.5 ma. Period: 5 minutes. Atropine here produced multiple small papules over the treated area but no flare (fig. 1A). This was repeated on another site at 11:30, the atropine producing slight itching with minute punctate reddish areas appearing followed by papules but again no flare. At 12:10 all the papules had disappeared. 1:1000 mecholyl chloride was now administered electrophoretically. Area of electrode: 5 sq. cm. Current: 1 ma. Time of administration: 5 minutes. The method in which the Mecholyl was applied to the atropinized area is illustrated in Fig. 1B. Note the inhibition zone of the atropinized area. The atropinized area shows no vasodilatation following Mecholyl but the non-atropinized zone shows typical vasodilatation. A suitable control was run in which the whole Mecholyl containing electrode was placed over the entire atropinized area. In this case, there was little or no change in color caused by the Mecholyl over the entire area. Other controls were run over an area not treated by atropine but an area of the skin electrophoretically treated with

physiological salt. The area treated by the electrophoresis of salt showed no inhibition of Mecholyl. In other words, the electrical current itself, had no effect on the subsequent application of Mecholyl to the skin.

Subject: M. B. One area of the skin was treated electrophoretically with tap water and another area with atropine sulfate at 11 A.M. Area of electrode: 10 sq. cm. Current: 0.5 ma. Time: 5 minutes. There was no irritation immediately after the current but there was slight redness of the skin after thirty minutes. This redness, however, disappeared in another 30 minutes. Following this, a solution of 1:10,000 mecholyl chloride was administered over the same electrode area with the same current and the same time as the tap water control. The passage of current through the skin did not inhibit the Mecholyl but inhibition of the Mecholyl reaction occurred in the atropinized area. In this experiment, a prolonged effect of the atropine on the skin was noted. The area treated in the morning was still blanched eight hours later although the surrounding area treated with the Mecholyl showed the redness

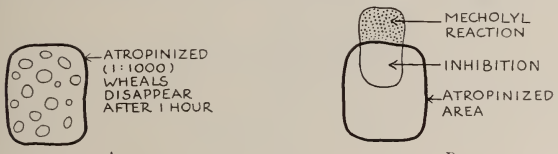

FIG. 1

of the vasodilatation produced earlier in the afternoon by the electrophoresis of the Mecholyl. It seems likely that the atropine formed depots in the skin in the same way that it has been observed for histamine (5).

In many experiments, it appeared that the inhibition by the atropine was not uniform chiefly because of atropine mottling effects. In experiments in which care was taken to eliminate secondary effects due to irritation, reddish mottling of the atropine treated area was not observed.

The action of atropine on the flare. If the flare following the administration of histamine is produced by an acetylcholine-like substance at the nerve endings it is possible that the inhibitory effect of atropine on the vasodilatation produced by Mecholyl would also be observed in the flare of the histamine wheal.

Subject: G. E. Atropine 1:5000 was administered with an electrode 4 sq. cm. in area. Current: 0.5 ma. for 5 minutes. There was reddish mottling of the skin with reddish papules but no flare. After one hour, 1:100,000 histamine was administered adjacent to the zone of the skin treated with atropine. The edge of the electrode containing the histamine was contiguous with the edge of the area that had been treated with Metholyl. The area of the electrode was 3 sq. cm. Current: 1 ma. for 3 minutes. As indicated in the figure, there was no inhibition of the histamine flare in the area of the skin treated with atropine.

In another experiment, atropine was injected intradermally and a histamine

wheal produced adjacent to the intradermally treated area. In this case also after 30 minutes there was no inhibition of the flare.

How may this be interpreted? If the flare is produced by the liberation of acetylcholine and, as we have demonstrated, atropine introduced electrophoretically readily inhibits the dilator effects of an acetylcholine-like substance, in our experiments, Mecholyl, it could have been anticipated that the flare should be inhibited by atropine. However, this has not been the case. There was no inhibition by the atropine. According to Dale (7), it is conceivable that the liberation of acetylcholine by the nerves might not be inhibited by the subsequent administration of atropine. However, the diffusion of atropine under the conditions of our experiments has been sufficient to take care of the liberation of acetyl-choline-like substances unless it be postulated that a membrane impermeable to atropine prevents the atropine from reaching the blood vessels which respond to the axon reflex. A mechanism of this type appears to us to

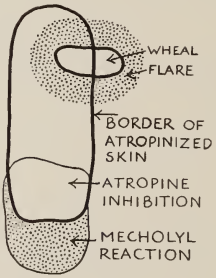

Fig. 2

be unlikely and we believe that this experiment is evidence that the vasodilatation produced by the axon reflex in this instance is not caused by an acetylcholine-like substance.

The effect of atropine on the wheal and flare of Urticaria solare. A case of Urticaria solare which has been studied in detail by one of us (8) was the subject of examination of the effect of atropine on the response of the skin to ultraviolet light. Under ordinary circumstances, if the patient in question is irradiated with light of sufficient intensity at 3700 Å and below, the skin responds with a wheal and a flare.

An electrode approximately 8 sq. cm. in area was saturated with 1:1000 atropine sulfate and applied to the skin with 0.5 ma. for 5 minutes. The skin responded with redness and a few papules. There was also a slight flare. About one hour after the skin was treated with atropine in this way, there were practically no traces of the atropine effect left in the skin. At the lower part of the area (fig. 2) 1:1000 Mecholyl was introduced by electrophoresis to ascertain if the atropine protected the skin against the Mecholyl reaction. The area of

the electrode was 10 sq. cm. and the current of 0.5 ma. flowed for 3 minutes. Examination for the presence of the atropine effect in this way revealed inhibition of the Mecholyl reaction. The upper part of the atropine treated area was now irradiated with ultraviolet. The atropine treated area irradiated in this way responded with a typical wheal and flare (fig. 2). The flare and wheal both extended into the atropine treated area and the rate of appearance of the wheal and the nature of the flare and wheal were the same as that ordinarily observed in this patient over areas in the skin not treated with atropine. In other words, the presence of atropine did not prevent the whealing and flaring reaction of the skin.

If, as it is contended (1, 2), the liberation of acetylcholine-like substance and its effect on a histamine release mechanism is responsible for the whealing and flare reaction in certain cases of the hypersensitiveness to physical stimuli, there is no evidence in this case that an acetylcholine substance is responsible. On the contrary, the case is ideal for the study of a release mechanism of this sort because the ultraviolet light is absorbed by the superficial layers of the skin and does not penetrate deeply the way heat or cold might. The atropine was given a full hour to diffuse into all regions of the skin, the concentration of the atropine was high enough to produce slight whealing and redness and a flare by virtue of its own effect. We believe, therefore, that in the case of the wheal in Urticaria solare as well as the flare our data do not lend evidence to the point of view that an acetylcholine-like substance is responsible for the production of such a wheal.

DISCUSSION

Although we have shown by means of the electrophoretic technic (a) the inhibition of acetylcholine-like (mecholyl-doryl) reactions of the skin and (b) the absence of any effect on the erythema and whealing response to light by atropine, there still remains to be studied by our method the inhibition of urticarial responses provoked by heat, cold, psychical stimuli, electrical responses, as well as other types which are characteristically allergic in nature.

Another method of studying the inhibition of the whealing response of the skin to drugs has been suggested by Alexander, Elliott, and Kirchner (4). These investigators found that there was a local skin refractoriness which occurred subsequent to the electrophoretic introduction of wheal forming drugs like pilocarpine and eserine. On the other hand, repeated electrophoretic introduction of histamine did not produce a refractoriness of the skin. The same was true of codeine, morphine, and atropine.

Hopkins, Kesten, and Hazel state that the urticaria and generalized eruption which may follow exposure to heat, physical exercise, emotional excitement, and the introduction of drugs is "cholinergic" in origin. They believe that this type of reaction is due to acetylcholine or closely related compounds released in the erupted area. According to Hopkins, Kesten and Hazel's paper, the essential abnormality of patients responding to heat with an urticarial reaction is that local administration of acetylcholine produces skin wheals. They believe

that the similarity of this response to the reaction of normal persons to histamine, fits in with the notion of Grant and his co-workers that the acetylcholine starts a chain reaction, one of the consequences of which was the release of an H-substance from the cells of the skin with the production of whealing.

Hopkins, Kesten and Hazel quote Dale to the effect that Dale has suggested that the flare which occurs about the histamine wheal and which is allegedly due to an axon reflex is, in all likelihood, the result of a secondary release of acetylcholine at the terminals of the reflex arc. According to our experiments, Dale's conception is not supported.

The point of view demanding that the wheals of chronic urticaria are formed incidental to a series of chain reactions involving acetylcholine-like substances could be tested by atropinizing large areas of the skin by the electrophoretic technic described in this paper.

We have not as yet studied the effect of atropinization of the skin on the whealing response to the electrophoretic introduction of allergens. Experiments of this type are in progress.

The oral or hypodermatic administration of atropine often results in generalized flushing of the skin. If the vasodilatation in the flushing of the skin were due to the liberation of a substance similar to acetylcholine, then the alleged acetylcholine reaction should have been inhibited by the atropine itself, indicating again that the vasodilatation is not entirely cholinergic.

SUMMARY

The effect of atropine on the mecholyl and whealing reaction of the human skin was studied by atropinizing areas of the skin by electrophoresis. A technic is described for studying the inhibition of Mecholyl in the skin by atropine. Suitable solutions of atropine sulfate introduced electrophoretically produce whealing and a flare. The electrophoretic introduction of high concentrations of atropine neither prevents the flare due to histamine nor the wheal and flare of Urticaria solare in atropinized sites; atropine does inhibit or abolish the local flush produced by Mecholyl or Doryl. The data do not support the point of view that the flare produced by histamine and the flare and wheal of Urticaria solare are part of a chain reaction involved in the liberation of an acetylcholine-like substance.

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BOECK'S SARCOID

A Report of Six Cases with One Necropsy[1]

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The exact nature of the clinical and histopathologic complex now generally designated as Boeck's sarcoid, or sarcoidosis, remains highly controversial. The nodular cutaneous lesions which originally occupied the attention of dermatologists were recognized by Boeck (1) in 1899 as part of a systemic disorder with lesions in the lymph glands, bones, mucous membranes and internal organs. Roentgenologic evidence of rarefaction of the bones of the hands and feet was described by Jüngling (5) as a not uncommon association of *lupus pernio*, a variant of cutaneous sarcoid. Both these observers felt that the disease was tuberculosis or closely related thereto. In 1915, Kuznitsky and Bittorf (3) called attention to the frequent presence of pulmonary lesions but emphasized the non-tuberculous character of the syndrome.

To Schaumann, (4) however, goes the distinction of recognizing the genetic identity of *lupus pernio*, Boeck's nodular and disseminated miliary sarcoid and its occurrence without skin manifestations. The histological picture was that of a "hard tubercle," i.e., large pale epithelioid cells, frequently surrounding multinuclear giant cells, absence of caseation, necrosis, calcification, severe tissue reaction or Koch's bacillus. Animal inoculations have been almost uniformly negative. Fibrous degeneration is common and assumes clinical importance when there is visceral dissemination of the sarcoid. Schaumann designated the disease "lymphogranulomatosis benigna", assumed a tuberculous etiology and cited several instances in which autopsies disclosed ultimate diffuse caseating tuberculosis. He explained the negative tuberculin reactions, unsuccessful guinea pig inoculations and failure to find tubercle bacilli as evidence of an anergic (Jadassohn) phase of tuberculosis. (7) He suggested that the cutaneous and visceral lesions may be due to a benign form of bovine tuberculosis. He further clarified the picture of diffuse miliary sarcoid infiltrations throughout the lungs and cited several instances of circulatory failure due to right heart strain or to actual myocardial infiltration with sarcoids.[2] As further proof of the wide systemic dissemination of the disease, the almost invariable presence of epithelioid tubercles in the tonsils was emphasized. The predilection for reticuloendothelial structures is indicated by the frequent infiltrations of liver,

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[2] Since completing this paper an important clinico-pathologic report on "Involvement of the Heart in Sarcoidosis or Besnier-Boeck-Schaumann Disease" by Professor Warfield T. Longcope and Dr. A. Murray Fisher has appeared. (J. Mt. Sinai Hosp., 8: 784, 1942). Of the relatively large series of 31 cases of sarcoidosis observed by Longcope and Fisher "six patients showed some evidence of myocardial insufficiency during life or sarcoids of the heart and pericardium were discovered at autopsy." This demonstrates the importance of heart involvement in sarcoidosis.

spleen, bone marrow and lymph nodes. (12) The radiating streaks from the hilar zones so frequently observed in the radiologic picture of pulmonary sarcoidosis are due to the concentration of sarcoid tissue in the lymphatic channels of the septa.

Clinical manifestations may be minimal or absent in the presence of roentgen evidence of extensive infiltration. On the basis of roentgen findings alone, however, it is often impossible to differentiate pulmonary sarcoidosis from miliary tuberculosis. The absence of caseation, calcification or significant physical signs tends to suggest the former condition. Pulmonary fibrosis superimposed on diffuse sarcoidosis will not infrequently result in a functional impairment of the right heart. Accentuation of the pulmonic second sound and right axis deviation in the electrocardiogram have frequently been observed.

The disease generally affects individuals of both sexes in the third and fourth decades and runs as a rule a relatively mild course; spontaneous resolution occurs in most instances. Fever is infrequent and constitutional symptoms are often minimal. The clinical picture of sarcoidosis is influenced by the character of the structures chiefly involved, e.g., skin, lymph nodes, lungs, bones, mucosae, tonsils, pituitary or salivary glands. The pulmonary hilar lymph nodes are very commonly enlarged and produce the classical "potato" configuration; bronchial compression with consequent atelectasis has been observed. Swelling and cyanosis of the fingers and toes are frequently produced by infiltrating sarcoids of the bones which give a roentgen picture of either fine punched-out areas or a delicate latticework. The predilection of sarcoids for the interstitial pulmonary tissue has been described. Several instances of diabetes insipidus due to sarcoid deposition in the pituitary have been recorded (8).

The blood picture has never been characteristic although a shift to the left is commmon. The sedimentation rate of the erythrocytes is frequently accelerated. An interesting phenomenon which sarcoidosis shares with lymphogranuloma inguinale, multiple myeloma and Kala Azar is an occasional hyperproteinemia with the increase solely in the globulin fraction. Snapper (13), in a recent monograph, found tuberculin and Mantoux reactions negative in eleven of his thirteen cases, and subsequent studies failed to disclose the development of tuberculosis in any of these instances. One case died of right heart failure due to the generalized pulmonary fibrosis of sarcoidosis. In the absence of any proof of the relationship of sarcoidosis to tuberculosis, Snapper interprets the picture as a peculiar reticulo-endothelial reaction with the formation of pseudotubercles under the influence of an unknown virus.

Aside from occasional response to scatter radiation, especially in lymphatic and parotid enlargements, therapy is chiefly supportive. Of various substances that have been recommended such as gold, arsenic, chaulmoogra oil and vitamins, arsenic alone may possibly have some value.

CASE REPORTS

Case 1. A 26 year old female diabetic presented diffuse adenopathy, paratracheal node enlargement and right heart failure due to diffuse pulmonary sarcoidosis. Biopsies of the skin and lymph nodes disclosed Boeck's sarcoid. Following two years of intermittent congestive failure she developed a severe nephrotic syndrome and amyloidosis.

History: (Adm. 483038). A white married woman, aged 23, was referred to the hospital by the Chest Clinic on February 21, 1938. She had been observed on the Medical Service on three previous occasions since the age of 12 for the control of an increasingly severe diabetes mellitus. An otitis media, at the age of 16, precipitated severe ketosis which was promptly controlled in the hospital. A year prior to admission, x-ray examination of the chest taken during an upper respiratory infection, disclosed distinctly enlarged hilar nodes. Four months later it was noted that the cervical nodes had enlarged and both parotids were palpable. She had, however, experienced no significant discomfort.

Examination: The patient was a fairly robust young woman who appeared much younger than her years. The skin was fair and smooth. The trachea was slightly deviated to the right. Moist râles were audible throughout both lungs but diminished following cough. The heart was not enlarged; the aortic and pulmonic second sounds were of equal intensity and no murmurs were detected. The blood pressure was 115 systolic and 75 diastolic. A firm notched spleen was felt four finger breadths below the left costal margin. The liver edge was barely palpable. Enlarged, discrete, firm, non-tender nodes which were not adherent to the skin and varied in size from a pea to a plum were present in both axillae and groins, the right submaxillary fossa and the left supraclavicular space.

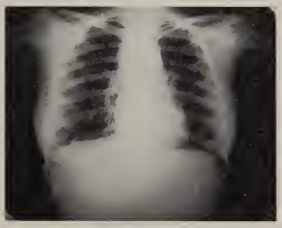

Fig. 1. Case 1. E. H. April 22, 1937. Chest roentgenogram showing moderate enlargement of hilar nodes

Laboratory data: The tuberculin reaction was positive only in dilutions of 1:10,000. Blood Wassermann reaction, negative. Hemoglobin, 85 per cent; leucocytes, 5,200 with a normal differential count.

Course: A biopsy of an inguinal node revealed "non-caseating epithelioid cell tuberculosis or Boeck's sarcoid." This was verified by a second biopsy. Guinea pig inoculation of a portion of the node failed to produce any lesion. A chest roentgenogram (fig. 1) disclosed moderate enlargement of the hilar nodes and a normal cardiac configuration. She was discharged to the Chest Clinic on March 5, 1938 with her status essentially unaltered.

She was readmitted to the Hospital on October 19, 1938. Progressive weakness, weight loss, intermittent cough and a fever ranging from 99° to 101°F. had been present since her discharge. A rash consisting of fawn-colored, discrete, raised plaques about 1 cm. in diameter appeared over the skin of the chest, back and arms several months prior to admission. A biopsy of one of the skin plaques in the Out-Patient Department, disclosed "non-caseating tubercles as seen in Boeck's sarcoidosis." The insulin requirement had risen to 65 units of protamine zinc daily and reactions had become frequent.

Examination: There was distinct evidence of weight loss and moderate pallor. There was a generalized maculopapular eruption, reddish-brown in color with fine adherent scales. There were several small pseudofollicles in the right lower conjunctiva. The sclerae were bluish. The upper lids were somewhat puffy. Numerous pin-point vesicles were present over the soft palate and buccal mucosa. Both parotid glands were enlarged and firm. Lymphadenopathy was generalized. A firm, non-tender liver descended 2 cm. below the

free border of the ribs. The spleen had enlarged considerably, now extending well below the umbilicus. There was slight clubbing of the fingers and toes.

Laboratory data: Blood: Urea nitrogen, 17 mg. per cent; cholesterol, 235 mg. per cent; cholesterol ester, 60 mg. per cent; glucose, 135 mg. per cent; total protein, 5.7 gm.; albumin, 3.4 gm.; globulin, 2.3 gm. per cent. Hemoglobin, 98 per cent. White blood cells, 6,700 with a differential count of polymorphonuclear segmented cells, 61 per cent; non-segmented, 8 per cent; lymphocytes, 18 per cent; monocytes, 8 per cent; eosinophiles, 4 per cent; basophiles, 1 per cent. The Mantoux test was positive, 1:100,000. The erythrocyte sedimentation rate was 1 hour and 49 minutes. The venous pressure was 4 cm. of water with no rise on right upper quadrant compression. The saccharin time was 14 seconds. Urine: A trace of albumin and moderate glycosuria; many hyaline and granular casts and occasional leucocytes; numerous calcium oxalate crystals were noted, but no casts. Stools, negative

FIG. 2. Case 1. E. H. Section of inguinal lymph node showing tubercles consisting of epithelioid and giant cells

for blood. Roentgenograms of the hands and feet disclosed no abnormality. Vital capacity test, 1000 cc. Biopsy of an inguinal lymph node (fig. 2) revealed "numerous tubercles consisting of epithelioid cells and giant cells." The electrocardiogram disclosed no definite abnormality. A chest roentgenogram (fig. 3) revealed a distinct increase in the cardiac configuration as compared with the film made on the previous admission; the lungs were studded with innumerable tiny miliary deposits and there was enlargement of the right paratracheal lymph nodes. A roentgenkymogram showed slight irregularity in the pulsations in the supra-apical portion of the left ventricle, presumably due to pleuropericardial adhesions.

Course: The temperature rose nightly to 101°F. for the first week and then became normal. Although sarcoid tissue is usually not radiosensitive, roentgen-ray therapy was applied to the nodes of the right axilla with subsequent diminution in their size but increased firmness in their consistency. The exposed skin lesions also underwent regression. Her general condition was markedly improved and at the time of discharge the skin lesions had practically disappeared. The hepatosplenomegaly, however, remained unchanged. Guinea pig inoculation with material from lymph nodes failed to produce any evidence of

tuberculosis. It was felt that the clinical picture was that of Boeck's sarcoidosis. A chronic disseminated tuberculosis could not, however, be excluded, but the duration, absence of caseation and tubercle bacilli and the negative guinea pig inoculation tended to minimize this possibility. She was discharged improved on November 20, 1938.

Almost immediately after her discharge, gradually increasing edema of the ankles was noted. Orthopnea then ensued and she developed a dry hacking cough. Marked albuminuria was noted in the Out-Patient Department. As amyloidosis was suspected, she was given liver and thyroid extract. Because of her progressive deterioration, she was readmitted to the Hospital on April 1, 1940.

Examination: There was severe orthopnea, cyanosis and generalized edema. Considerable fluid was present at the left pulmonary base. The heart was enlarged, the rate was rapid and a loud gallop rhythm was audible at the apex; a low pitched systolic murmur was audible over most of the precordium; the pulmonic second sound was sharply accentuated. There was moderate ascites and massive edema of the legs. The liver and spleen both descended 3 cm. below the costal margins.

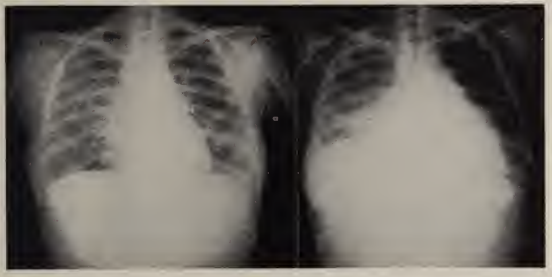

FIG. 3 FIG. 4

FIG. 3. Case 1. E. H. March 22, 1938. Chest roentgenogram showing diffuse miliary deposits. The paratracheal lymph nodes are more prominent and the heart has enlarged slightly.

FIG. 4. Case 1. E. H. April 4, 1940. Heart markedly enlarged. Resolution of miliary lesions. Right pleural exudate

Laboratory data: Blood: Hemoglobin, 117 per cent; red blood cells, 6,140,000; leucocytes, 4,550 with a differential count of 56 per cent polymorphonuclear neutrophiles, 24 per cent lymphocytes, 8 per cent eosinophiles, 10 per cent monocytes and 2 per cent basophiles. Blood urea nitrogen, 18 mg. per cent; cholesterol, 310 mg. per cent; cholesterol ester, 170; glucose, 150 mg. per cent; total plasma protein, 4.5 per cent; albumin, 3 per cent; globulin, 1.6 per cent. Icteric index, 6. Takata Ara, 4 plus. Urine: cloudy; acid; specific gravity, 1.028; albumin, 2 plus; sugar, a trace; Esbach, 1 gm. per liter. The basal metabolic rates varied from 0 to minus 10 per cent. The Congo red test for amyloidosis, disclosed 35 per cent tissue absorption in one hour. The electrocardiogram showed sinus tachycardia, right axis deviation, QRS of low voltage, R_2 very low, T_2 isoelectric, T_3 inverted. Subsequent tracings disclosed higher T waves and an isoelectric T_4. The venous pressure was 14 cm. of water with a rise to 20 cm. on right upper quadrant pressure. The saccharin time was 22 seconds. A tuberculin test was positive in a dilution of 1:100,000. The sedimentation time was 1 hour and 29 minutes. Skin tests for brucellosis were negative. A chest roentgenogram disclosed marked resolution of the miliary lesions in the lungs noted in September 1938; an infiltration in the left cardiophrenic angle was seen. There was evidence of a recent exudation in the pleura over the entire right lung; the heart was markedly enlarged (fig. 4); the lymph nodes in the right paratracheal space were diminished in size

as compared with the previous film. X-ray examination of the hands showed no bone abnormality.

The picture of right heart failure which she presented on admission was presumably secondary to a *cor pulmonale* resulting from extensive pulmonary sarcoidosis with the production of chronic interstitial fibrosis. The secondary polycythemia, the marked accentuation of the pulmonary second sound, the marked right axis deviation as indicated in the electrocardiogram and the distinct elevation of the venous pressure with right upper quadrant compression all confirmed this impression. The hypoproteinemia and albuminuria indicated a nephrotic syndrome of obscure etiology. The Congo red test tended to exclude amyloidosis. Other possible interpretations were diabetic glomerulosclerosis, pressure on the renal veins by masses of nodes and sarcoidosis of the kidney.

Course: With restriction of fluids, ammonium chloride and frequent injections of esidrone, there was a weight loss of 25 pounds within a month and the patient's condition was greatly improved. The diabetes was adequately controlled with protamine zinc insulin. The venous pressure on discharge was 6 cm. with a rise to 12 cm. on right upper quadrant pressure; the saccharin time fell to 17 seconds. Although all evidences of congestive failure disappeared, the polycythemia (hemoglobin 128 per cent, red blood cells 6,580,000) and the hepatosplenomegaly persisted. She was given maintenance doses of digitalis and referred back to the Chest Clinic.

With a regimen of marked restriction in activity she was fairly comfortable until June 1941 when it was noted that the esidrone was becoming less effective in relieving the edema and that she was growing increasingly dyspneic. Intermittent pleural effusions had been present but the roentgen picture was otherwise unchanged. The blood cholesterol was 410 mg. per cent; blood protein, 5.4 gm. per cent; albumin, 2.4 gm.; globulin, 3.0 gm. The circulation studies were normal. A Congo red test was not conclusive.

At the time of writing she is again in the Hospital with what appears to be a nephrotic syndrome, based on either amyloidosis or a secondary hypoproteinemia due to renal infiltration with Boeck's sarcoid. On 65 units of protamine zinc insulin and 300 grams of carbohydrates, she spills considerable glucose but there is no acetonuria. With the rise of Congo red retention to 90 per cent the presence of amyloidosis appears established. Urinary concentration tests remain normal.

Comment: A curious syndrome which is now firmly established as a form of sarcoidosis had been, until recently, variously designated as uveoparotid fever, uveoparotitis (11) and uveoparotid tuberculosis (6, 9). First described by Heerfordt (2) in 1899, numerous case reports appeared in the Scandinavian literature and the disease was ascribed, in turn, to leprosy, mumps, syphilis and tuberculosis. The clinical picture is characterized by a subfebrile course, usually of many months duration with ultimate gradual subsidence, uveitis, generally bilateral, enlargement of both parotids and frequently of the submaxillary and submental glands and rare facial paralysis, due to parotid compression of the facial nerve. Numerous instances of diffuse pulmonary infiltration, at times miliary in type, and enlargement of the mediastinal lymph nodes have been recorded. Constitutional symptoms are, as a rule, minimal. Permanent visual impairment as a result of injury to the uveal tract presents the greatest danger. Although pulmonary infiltration, mediastinal gland enlargement, generalized adenopathy and lesions with a histologic picture of a benign lymphogranulomatosis had been recognized early, it is to Slot in 1936 and Longcope (10) in 1937 that we owe the present knowledge of the identity of the Heerfordt syndrome and Boeck's sarcoid. *Per contra* numerous instances of Boeck's sarcoid with iridocyclitis, uveitis and parotid swellings have been reported.

Of Longcope's 31 cases of sarcoidosis, 13 disclosed uveal tract involvement and 8 presented an uveoparotitis (15). The histologic picture, it is now recognized, is identical with that of sarcoidosis, i.e., a "hard tubercle", similar in size to a miliary tubercle, consisting of large polygonal pale-staining epithelioid cells and occasional multinuclear giant cells; there is absence of necrosis and minimal tissue reaction. Despite the widely held belief that the disease is of a tuberculous nature, animal inoculations of affected tissues have been largely unsuccessful. Tubercle bacilli have rarely, if ever, been recovered from the lesions and tuberculin reactions are rarely positive. A number of instances have been reported, however, of the simultaneous presence of uveoparotitis and tuberculosis in the same individual and in two instances, death from miliary tuberculosis ensued. The following case is a classical example of the group hitherto designated as uveoparotid fever.

Case 2. A 34 year old housewife presented the syndrome of uveoparotitis with parotid swellings, generalized adenopathy with hilar gland enlargement and impaired vision as a result of uveal tract involvement. Sections from lymph nodes, tonsil, and iris disclosed Boeck's sarcoid.

History: (Adm. 414452). A 34 year old housewife, a native of Ireland, was admitted to the hospital on September 23, 1937. She had been in apparently good health until nine months preceding admission when gradually increasing fatigability, progressive weight loss and anorexia appeared. For the next few months these symptoms increased and weakness was profound. Three months prior to admission, she noted painless bilateral swelling of both parotid glands which reached considerable size. A temperature fluctuating between 100° and 102°F. appeared shortly thereafter. Diminished visual acuity and bilateral scotomata had been present for several months, but were now followed by distinct blurring and photophobia. Following a study at the Consultation Service, she was given eight roentgen treatments to the neck and chest with rapid subsidence of the parotid swellings. She had not menstruated for four months. Drenching night sweats had appeared but had gradually subsided. She had lost 30 pounds in weight. She also complained of stubborn constipation, moderate urinary urgency and nocturia, intermittent headaches, tinnitus aurium and occasional vomiting.

Examination: The patient was a well nourished, somewhat sallow woman. The eyes presented a pericorneal violaceous injection and the cornea was somewhat hazy; the pupils responded poorly to light and also in accommodation. The fundi presented a red reflex but no details were visible. There was definite evidence of a bilateral uveitis with reduced vision, ciliary injection, deposits on Descemet's membrane and increased reluecncy of the anterior chamber. With the suspicion that the condition was of a tuberculous nature, a number of intracutaneous injections of tuberculin had been given in an attempt to desensitize. With these injections there was neither a focal, nor a systemic reaction. A profuse, purulent postnasal drip was seen; the tonsils were markedly enlarged and cryptic. The parotid glands were no longer felt. The chest configuration was normal with an increase in retromanubrial dulness to both right and left. Low pitched systolic murmurs were audible at the cardiac apex and base. The liver edge descended 3 cm. and the splenic edge 1 cm. below the costal margin. There were several small pea-sized discrete inguinal glands. The blood pressure was 120 systolic and 92 diastolic.

Laboratory data: Blood: Hemoglobin, 84 per cent; leucocytes, 6,400 with segmented polymorphonuclear neutrophiles, 41 per cent; non-segmented, 40 per cent; lymphocytes, 10 per cent; monocytes, 7 per cent; eosinophiles, 1 per cent; basophiles, 1 per cent. Blood chemistry: Urea nitrogen, 10 mg. per 100 cc.; uric acid, 1.6 mg. per cent; glucose, 100 mg. per cent; total plasma proteins, 6.8 per cent; albumin, 2.2 per cent; globulin, 4.6 per cent; cholesterol, 580 mg. per cent; cholesterol ester, 415 mg. per cent. Takata Ara, negative. Wassermann reaction, negative. The urine disclosed a faint trace of albumin with microscopic evidence of occasional leucocytes and coarse granular casts.

A chest roentgenogram (fig. 5) disclosed normal pulmonary fields; the heart was normal in size and shape; shadows were observed in both hilar regions with marked enlargement of the right paratracheal glands, suggesting lymphatic neoplasm. X-ray examinations of the knees, lumbo-sacral spine and both shoulders failed to disclose any bone abnormality. A chest x-ray examination, six weeks later, failed to reveal any alteration. The electrocardiogram showed sinus tachycardia and low T waves. A tonsil biopsy (fig. 6) revealed, in addition to hypertrophic tissue, one epithelioid cell tubercle.

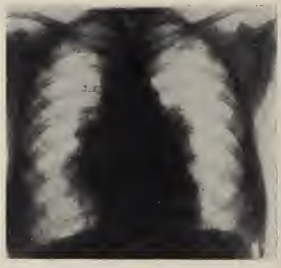

FIG. 5. Case 2. A. S. Chest roentgenogram; enlargement of hilar nodes

FIG. 6. Case 2. A. S. Biopsy of tonsil showing one epithelioid cell tubercle

Course: During the six-week period of observation, the patient was afebrile. There was no alteration in the visual status and repeated roentgenograms of the mediastinum revealed no alteration in the hilar shadow. With the finding of increased intraocular pressure in the left eye, an iridectomy was performed. The specimen (fig. 7) disclosed several epithelioid cell tubercles in the iris. She was discharged on November 7, 1937 with the diagnosis of uveoparotitis (Heerfordt syndrome) but was later re-classified, with the growing recognition of this syndrome's relationship to systemic sarcoidosis, as a case of Boeck's sarcoid.

Case 3. A 26 year old white woman developed fever, arthralgias, transient albuminuria and hypertension in the eighth month of pregnancy and was found to have rheumatic valvular disease. Labor was induced. A chest roentgenogram disclosed marked bilateral hilar adenop-

athy and a biopsy of a supraclavicular node showed Boeck's sarcoid. She has been remarkably free of symptoms.

History: (Adm. 467870). A 26 year old married housewife was admitted to the Hospital on January 14, 1941, referred by the Chest Clinic. She had been in excellent health until eight months before, when in the eighth month of her first pregnancy, she experienced diffuse arthralgias, headaches, a low grade fever and intermittent scotomata. Moderate hypertension and albuminuria were detected and she was admitted to The Woman's Hospital for the induction of labor; she was delivered of a normal infant. She was urged to restrict her activity and remain under close supervision. On returning home, ankle edema became pronounced, she became quite asthenic, and firm reddish swellings appeared over the skin of the legs and hands. She complained of occasional precordial discomfort and palpitation. Shaking chills with temperature rises to 103°F. persisted for several weeks.

FIG. 7. Case 2. A. S. Biopsy of iris with several epithelioid cell tubercles

She returned to her native town of Indiana, Pennsylvania and was admitted to the local hospital. A chest roentgenogram was reported as disclosing "no evidence of lung parenchyma or pleural involvement but considerable bilateral paramediastinal adenopathy with sharply defined borders suggesting a possible juvenile type of specific tuberculous infection with glandular involvement." The tuberculin test was reported as negative, the sedimentation rate somewhat accelerated and blood and urine studies normal. With the subsidence of her symptoms, she returned to New York and was observed in the Cardiac Clinic because of the precordial pains, exertional dyspnea and cough. A chest film disclosed the paramediastinal shadow previously described and she was referred to the hospital.

Examination: The patient was a fairly well nourished woman in no apparent distress. There were several discrete, slightly tender nodes about 1 cm. in diameter in the right supraclavicular fossa and many pea-sized shotty nodes throughout both anterior and posterior cervical zones. Several hard inguinal nodes were also present. A presystolic murmur and thrill were heard within the cardiac apex and followed by the shock of a sharp first sound. The pulmonic second sound was accentuated. There were numerous premature contractions. The blood pressure was 115 systolic and 82 diastolic.

Laboratory data: Blood: Hemoglobin, 90 per cent; red blood cells, 5,000,000; platelets, 370,000. Differential: non-segmented polymorphonuclear neutrophiles, 27 per cent; segmented, 31 per cent; lymphocytes, 25 per cent; eosinophiles, 2 per cent; basophiles, 1 per cent; monocytes, 14 per cent. The increase in non-segmented neutrophiles and the monocytosis suggested a chronic infection. Sternal bone marrow studies revealed a normal picture. The sedimentation rate was 2 hours and 48 minutes. The Mantoux test was negative in a dilution of 1:100,000 but positive in a dilution of 1:1,000,000. The urine was negative; concentration and dilution tests were normal. A chest roentgenogram revealed large globular shadows at both hilar areas which had the appearance of lymph nodes as found in Boeck's sarcoid. The electrocardiogram revealed sinus arrhythmia, right axis deviation and frequent auricular ectopic beats. Biopsy of a supraclavicular lymph node disclosed the histologic picture of Boeck's sarcoid.

Course: Aside from slight precordial discomfort and rare exertional dyspnea, the patient was comfortable during her hospital stay. There was no elevation of temperature. She was referred to the Chest Clinic and was last seen on March 10, 1941, at which time she had no complaints. Several small nodes were still present in both supraclavicular regions.

Case 4. A 37 year old negress submitted to the removal of a submental lymph node which had gradually enlarged after remaining stationary for 6 years. Biopsy of this node and subsequently of an axillary node disclosed the histologic picture of Boeck's sarcoid. She was almost entirely asymptomatic and roentgen studies of the lungs and extremities were negative. The Mantoux reaction was positive.

History: (Adm. 477415). A 37 year old married colored woman was admitted to the Medical Service on August 8, 1941. A plum-sized submental swelling which had not materially altered for six years, suddenly enlarged five months prior to admission and was removed for cosmetic reasons. A section of what proved to be a lymph node disclosed Boeck's sarcoid. A month later a similar swelling appeared in the left axilla. Aside from transient weakness and fatigability there had been no discomfort. All laboratory studies including x-ray examinations had been negative.

Examination: The patient was a comfortable well nourished negress. The skin was clear. The trachea was in the midline and freely movable. The submental scar was well healed. A grape sized non-tender movable node was felt in the left axilla; no other glandular enlargement was noted. The lungs were clear and no increase in retromanubrial dulness was detected. The heart disclosed no abnormality. The blood pressure was 140 systolic and 90 diastolic. The splenic edge was felt at the costal margin.

Laboratory data: Blood: Hemoglobin, 75 per cent; white blood cells, 21,050; segmented polymorphonuclear neutrophiles, 68 per cent; non-segmented, 2 per cent; lymphocytes, 20 per cent; monocytes, 6 per cent; eosinophiles, 4 per cent. Urine examination was negative. A chest roentgenogram disclosed no abnormality. X-ray examinations of the bones of the hands and feet were negative. The electrocardiogram was normal. The blood Wassermann reaction was negative. The sedimentation time was 60 minutes. The tuberculin test (Mantoux) was strongly positive, 1:100,000. Biopsy of the axillary nodes confirmed the diagnosis of Boeck's sarcoid.

The patient was asymptomatic in the hospital with a single temperature rise to 100.4°F. When seen at the Follow-Up Clinic on October 20, 1941 she had no complaints and had gained ten pounds in weight. There were no palpable lymph nodes and the spleen was no longer felt.

Case 5. A 59 year old Jewish woman began to suffer from lymphadenopathy in and below the neck. Biopsy revealed typical Boeck's sarcoid. Bouts of fever had been intermittent for almost a year. The cervical lymph nodes had become huge, displacing the trachea and compressing the veins. Hepatosplenomegaly appeared. The response to intermittent radiotherapy was striking with complete disappearance of the mass in the neck within two weeks and rapid improvement in symptoms.

History: (Adm. 483511). A 59 year old Russian housewife was admitted to the Hospital on December 23, 1941 complaining of malaise of eighteen months duration and swelling of the left side of the neck for about one year. Aside from frequent colds and an occasional sore throat her health was apparently good. The onset of her illness was gradual and characterized by weakness, nausea with occasional vomiting, anorexia and loss of weight. Gastro-intestinal roentgen studies were negative. The nausea and vomiting gradually subsided. A year before admission a grape-sized lump was noted in the left infraclavicular space. She went to Florida and regained considerable weight and strength. The mass soon increased in size, however, and her symptoms recurred. She was studied at the Consultation Service where a biopsy of the mass disclosed the histologic picture of Boeck's sarcoid. No specific treatment was instituted. For six months prior to entry she had had intermittent febrile episodes with temperature elevations to 102°F., lasting from three to four days and followed by afebrile periods of a week's duration. Weakness soon became pro-

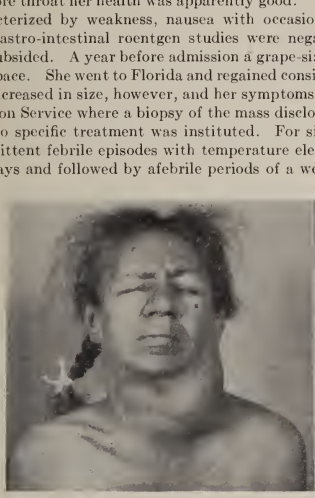

FIG. 8

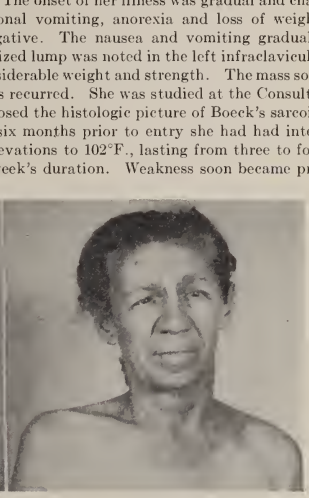

FIG. 9

FIG. 8. Case 5. R. F. Sarcoidosis of cervical nodes
FIG. 9. Case 5. R. F. Disappearance of huge cervical nodes after two weeks of roentgenotherapy

nounced, drenching night sweats appeared and the weight loss reached 35 pounds. The mass in the left side of the neck had become huge.

Examination: The patient was a thin chronically ill woman with marked enlargement of the left side of the neck which appeared to force the mandible upward (fig. 8). The consistency of the mass was rubbery and suggested a confluent collection of lymph nodes. Pea-sized nodes were also palpable in the right cervical area and in the left axilla. There were dilated veins over the left shoulder. The trachea was markedly displaced to the right. The lungs were clear. The heart was of normal size and no murmurs were audible. The pulmonic and aortic second sounds were of equal intensity. The blood pressure was 124 systolic and 76 diastolic in both arms, although the left radial pulse appeared somewhat smaller than the right. A firm rounded splenic margin was felt 2 cm., and the liver was palpable 3 cm. below the costal margin.

Laboratory data: Blood: Hemoglobin, 88 per cent; leucocytes, 7,200; segmented polymorphonuclear neutrophiles, 43 per cent; non-segmented, 23 per cent; lymphocytes, 23 per cent; monocytes, 10 per cent; plasma cells, 1 per cent. The sedimentation time exceeded 2 hours. Urea nitrogen, 8 mg. per cent; uric acid, 3.9 mg. per cent; cholesterol, 245 mg. per cent; cholesterol ester, 160 mg. per cent; glucose, 90 mg. per cent. Blood Wassermann reaction, negative. The urine showed a faint trace of albumin but was otherwise normal; Bence Jones protein absent. Total plasma proteins 6.3, albumin 5.0, globulin 1.3 mg. per

cent. X-ray examination of the chest did not reveal any abnormalities in the lymph nodes or lungs. Roentgen-ray examination of the extremities failed to show the bone changes characteristic of Boeck's sarcoid. The venous pressure was 17 cm. of water in the left arm compared with 8 cm. in the right arm. There was no rise on right upper quadrant pressure.

Course: Although, as previously stated, Boeck's sarcoid is deemed radioresistant by most observers, our own somewhat encouraging results with roentgen therapy (cases 1, 2, and 6) suggested its further trial. The results were quite remarkable with complete disappearance of the huge neck mass within two weeks (fig. 9). The temperature became normal, her strength returned rapidly and she gained weight. The hepatosplenomegaly, however, persisted.

Case 6. This patient had an obscure undiagnosed skin condition over a period of twenty-four years, which probably was Boeck's sarcoidosis. She suffered from repeated attacks of arthralgia, a persistent cough, dyspnea, transient edema of the legs, prolonged iridocyclitis, and enlarged hilar lymph nodes. Subsequently she developed supraclavicular lymph nodes; biopsy of one of these disclosed the histology of Boeck's sarcoid. Finally she developed an enlarged spleen and an abdominal mass which proved to be radiosensitive. She died with the picture of edema, ascites, pulmonary edema and a terminal pneumonia. Necropsy revealed the end stage of Boeck's sarcoid.

History: (Adm. 390977). A 59 year old married woman entered the Hospital for the first time on March 16, 1936 because of progressive asthenia, and palpable supraclavicular lymph nodes. One of these supraclavicular nodes was removed by Dr. Neuhof for biopsy, and the report was "tuberculous lymphadenitis, large cellular (Ziegler) type."

She had been suffering for years from a pruriginous macular skin condition, beginning about 1914. She had consulted distinguished dermatologists, one of whom made a diagnosis of "prurigo nodularis." In 1934 she suffered from edema of the feet, and joint pains, and a diagnosis of chronic arthritis was made. That same year she had a persistent nonproductive cough, and some dyspnea. Still later she had a unilateral pretibial skin lesion which resembled an erythema nodosum. In April, 1935 she had a severe prolonged bilateral iridocyclitis of unknown etiology. At that time tests for syphilitic and for gonorrheal infection were entirely negative. X-ray examination of the chest in 1936 revealed enlarged hilar lymph nodes.

Following her discharge from the Hospital she improved somewhat and gained weight. Although she returned to her work as a buyer, her energy was appreciably impaired. Exertional dyspnea, occasional tinnitus aurium and slight ankle edema soon developed. With the appearance of lymphadenopathy, involving the cervical, axillary and inguinal regions, she was given several roentgen-ray treatments with rapid reduction in the size of the nodes. The skin lesions, consisting of fawn-colored macules associated with pruritus, rapidly increased in number. One month prior to her second admission to the Hospital, i.e., January 10, 1938, she had a respiratory infection with severe cough, fever, arthralgia and malaise. Abdominal cramps were intermittent. Weakness became pronounced and she was dyspneic even on mild exertion. She was distressed by a dull nagging pain in the left upper abdomen.

Examination: There was evidence of moderate weight loss and marked asthenia; the skin was pale and sallow. Numerous round hypertrophic plaque-like scars were present on the arms and legs. They were more numerous over the lower portion of the limbs and on the extensor surfaces. Aside from a few small soft posterior cervical nodes, there was no adenopathy. Upper parasternal dulness was increased bilaterally. The heart was moderately enlarged; a soft systolic murmur was audible at the apex and a prolonged systolic murmur was heard over the base. Examination of the abdomen disclosed a tender, slightly irregular mass about the size of a lemon in the left upper quadrant; it extended to the costal arch, was apparently fixed to the underlying structures and did not move with respiration. Ankle edema was slight.

Laboratory data: Blood: Hemoglobin, 77 per cent; leucocytes, 4,500; segmented polymorphonuclear neutrophiles, 64 per cent; non-segmented, 6 per cent; lymphocytes, 28 per

cent; monocytes, 2 per cent. The urine was negative. The stools disclosed neither ova nor blood. Repeated examinations of the sputum failed to reveal tubercle bacilli.

Course: During her two weeks' stay the temperature ranged from 99° to 100°F. Four roentgen-ray treatments to the left upper abdomen produced rapid reduction in the size of the mass. The clinical picture was interpreted as a Boeck's sarcoid in remission, or a tuberculous lymphadenitis.

After a brief period of relative comfort following her discharge from the hospital, intermittent chills with temperature elevations to 104°F. appeared. This was soon followed by a persistent dry cough and substernal and precordial oppression.

She was admitted to the hospital for the third time on March 16, 1938 with evidence of further weight loss, marked pallor and moderate tachypnea. On the extensor surfaces of the right forearm there were four discrete elevated circular nodules about 1 cm. in diameter. Several urticarial wheals were present on the breast, abdomen and back. Firm, non-tender nodes were palpable in the right axilla and in both inguinal regions. Showers of fine râles were heard over the right pulmonary lobe. The retromanubrial dulness was further widened. Loud systolic murmurs were audible at the cardiac apex and base. The blood pressure was 116 systolic and 58 diastolic. The irregular tender mass in the left upper abdomen was somewhat larger, extending further mesially.

Laboratory data: Blood: Hemoglobin, 78 per cent; red blood cells, 4,660,000; leucocytes, 5,300; segmented polymorphonuclear neutrophiles, 46 per cent; non-segmented, 12 per cent; lymphocytes, 32 per cent; monocytes, 9 per cent; basophiles, 1 per cent. Wassermann reaction, negative. Subsequent blood counts indicated progressive anemia and leucopenia with only transient improvement following transfusions. The urine disclosed a faint trace of albumin.

Course: Although the temperature fell to normal within a week, deterioration was rapid. Enlarged nodes appeared in the cervical and axillary areas. The spleen was felt 3 cm. below the costal margin and evidence of diffuse pulmonary infiltration became evident. Several roentgen exposures did not materially influence the size of the lymph nodes or the abdominal mass. There were recurrent diffuse urticarial eruptions. Shortly after the appearance of extensive edema and ascites, pulmonary edema supervened and she died on June 12, 1938, three months after her last admission.

Necropsy findings: (Dr. Abou D. Pollack). Diffuse "sarcoidosis" was found in the lungs, lymph nodes, kidneys and spleen. Bronchopneumonia, terminal in character, involved all lobes. The liver was the seat of extreme fatty change and marked chronic passive congestion. The heart showed parenchymatous degeneration and atrophy; the coronary vessels were distinctly arteriosclerotic without narrowing. A calcified pulmonary infect was found in the right upper lobe and there were enlarged paratracheal lymph nodes. The interlobar pleural spaces contained thick fibrous adhesions. Although microscopic study of the lesions failed to disclose the epithelioid cell tubercles generally found in sarcoidosis, the peculiar hyaline bands found in the lymph nodes, spleen and lungs are identical with those frequently observed in the late stages of sarcoidosis.

Comment (Dr. Paul Klemperer): The histology of the lesion in this case is very puzzling. The original biopsy was diagnosed as tuberculosis of the Ziegler type which was suggestive of the diagnosis of "sarcoidosis." The post-mortem examination, however, did not show any evidence of any lesion which resembled the epithelioid cell tubercle found in "sarcoidosis." The most conspicuous feature was the peculiar hyaline bands found in lymph nodes, spleen and lungs. While they were not specific, they reminded one of the healing stage in tuberculosis. The study of several cases of undoubted "sarcoidosis" with typical skin and bone lesions has convinced me that the end stages of this morbid process are characterized by a hyalinization of exactly the same type as found in this case. The calcification present in this case was also found in others. Moreover, positive guinea pig inoculation of one of the lymph nodes in this case, while not entirely satisfactory (because accidentally no histological study of that particular node was made), offers a valuable argument in favor of the tuberculous nature of the entire morbid process.

DISCUSSION

Six cases of Boeck's sarcoid are herein described. Although the affection is said to be characterized by a generally benign course it is noteworthy that one patient has succumbed to diffuse visceral sarcoidosis, a second is completely invalided as a result of chronic right heart failure secondary to advanced pulmonary sarcoidosis and a nephrotic syndrome, and a third has suffered progressive loss of vision due to sarcoid infiltration of the uveal tract. On the other hand, two examples of sarcoidosis limited to peripheral lymph nodes without any systemic manifestations are also recorded. One instance with hilar and peripheral lymphadenopathy ran a relatively benign course. A patient, with huge lymphadenopathy involving the left cervical chain, who had intermittent fever, and lost considerable weight remains chronically ill. Histologic confirmation was attained in all cases by biopsies of either lymph nodes, tonsils, iris or skin. The autopsied case disclosed diffuse visceral sarcoidosis. The tendency of the disease to chronicity and spontaneous retrogression may at a particular time give a misleading picture of its extent.

Four of the six cases gave positive tuberculin reactions, albeit strong in only one instance. Tubercle bacilli were never found and associated active tuberculosis was never established. The hematologic picture was not unusual in any case and the sedimentation rate, contrary to the experience of some observers, was not accelerated. None of the cases disclosed the striking bone changes first described by Jüngling (5). As further evidence of the systemic dissemination of this disease in the absence of cutaneous lesions, three cases presented no skin manifestations. Although the disease is not usually associated with significant temperature elevations, two of our cases exceeded temperatures of 103°F. for relatively long periods. Iridocyclitis was present in two instances. Hyperproteinemia did not occur; a reversal of the albumin-globulin ratio appeared in the case with a nephrotic syndrome.

Although there is no known specific therapy for Boeck's sarcoid and most observers consider the lesions radioresistant, our experience with roentgen therapy has been very encouraging. Of four cases that received such treatment, three showed some improvement and in the fourth, a huge mass of cervical nodes disappeared within two weeks. It should be emphasized that radiosensitivity may vary with the stage of the disease. It is conceivable that in an involutionary phase the response may be much more prompt than when the disease is in the process of evolution and hence radioresistant. This is exemplified in Case 6 in which the cervical masses retrogressed under radiotherapy but subsequently were resistant with the wide dissemination of the disease preceding the patient's death.

Comment on Etiology: The cause of Boeck's sarcoid in spite of repeated efforts to ascribe it either to the tubercle bacilli or to an unknown virus still remains *unknown*. The histologic picture, to be sure, closely resembles that of tuberculosis, with certain exceptions. These, as previously emphasized, are the almost uniform absence of caseation, calcification and necrosis. On the other hand, one must recognize the not inconsiderable number of reported instances of ultimate tuberculosis developing in proven cases of Boeck's sarcoid (14). Vari-

ation in reactions to the tuberculin and Mantoux test would also tend to indicate that in sarcoidosis an anergic form of tuberculosis may be postulated. The anergic concept gains further support from Kyrle's (16) observation of the presence of tubercle bacilli in the early skin lesions and their gradual disappearance with the evolution of the disease. Toward the termination of the disease the appearance of active tuberculosis may again indicate a loss of the anergic quality which characterizes sarcoid.

CONCLUSIONS

1. A report of the manifold clinical pictures found in Boeck's sarcoid, based on the observation of six cases is presented.

2. The identity of uveoparotitis (Heerfordt's syndrome) and Boeck's sarcoid is emphasized.

3. The course of the disease in not invariably benign. Of the six cases herein reported, three terminated in severe disability and one terminated in death.

4. Contrary to the generally held opinion that Boeck's sarcoid is not radiosensitive, our results with radiotherapy have been very encouraging. Of the four cases that received such treatment all responded favorably.

5. The nature of the disease is unknown. Some evidence of its possible relationship to tuberculosis is discussed.

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INTELLECTUAL SYMPTOMS IN TEMPORAL LOBE LESIONS INCLUDING "DÉJÀ PENSÉE"*

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The purpose of this communication is to record two examples of the paroxysmal abnormalities of thought which sometimes result from the presence of lesions in one temporal lobe. Both cases show phenomena which are seen more or less commonly, and in addition, one (K.) displays a state which we would call "*déjà pensée*" and which seems not to have been described before. From the disturbances manifested by the two patients, as well as from previous experience, it is possible to derive some theoretical conclusions concerning one of the functions of the temporal lobes.

CASE REPORTS

Case 1. Episodes of sudden, unvolitional onset of thoughts, sometimes associated with nausea and vomiting and occasionally followed by a generalized convulsion. The thoughts seemed familiar (*déjà pensée*) although, at least according to the patient's conscious memory, they were really fictional, and there was no evidence that they had been thought before. However, the thoughts although fictional themselves, were on a general background of experience which was, in general, actual. In addition to the feeling of familiarity for the thoughts, in at least one instance one emotion was attached to the *déjà* phase of the fictional thought, and another to the thought itself.

K., a right-handed writer of 45, who had made many trips to South America, and who was referred to one of us by Dr. Joseph Stenbuck, had a meningioma of the left temporal lobe. He died after operation. The nature of the lesion was proved at autopsy.

K. described the fits as follows: he would suddenly and involuntarily begin to think of experiences in South America. He would think of people he had met there, of trips he had taken and of various incidents connected with these people and trips. Although he had actually made many such trips and had really met a great many people, the thoughts were not about the actual people he had met nor about actual incidents he had experienced. In other words, they were not real memories, but were fictions. Yet, the contents of the thoughts seemed familiar—seemed, in fact, like things that had happened. Frequently K. remembered the thoughts after the attack was over. The thoughts were always extremely vivid.

An emotion, usually an unpleasant one, accompanied the thoughts; often it was of ridicule.

One of K.'s examples concerned thoughts of a hunting trip. He thought of his comrades joking about his being short in stature. Although according to his subsequent conscious memory, this event had never occurred, nonetheless it seemed like an actual memory of a real episode during the attack. Accompanying the thoughts was a feeling of being ridiculed; yet the content of the thoughts themselves, the joking at K.'s expense, was full of humor, and the joking was plainly intended to be funny.

Not only did the thoughts come suddenly, but the patient added that they were never evoked as thoughts usually are, by someone or something he saw or heard, or by any experience he was having.

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* From the Neurological Service of Dr. I. S. Wechsler. Read at a meeting of the Harvey Cushing Society, May 19, 1942, New York. The term "déjà pensée" was suggested by Dr. Wechsler.

Often the thoughts were accompanied by nausea and vomiting and by a peculiar feeling different from nausea, in the hypochondrium; sometimes they were followed by a generalized convulsion.

There were occasional headaches at the vertex. Infrequently, there were brief periods during which he was unable to understand spoken language. There were no gustatory or olfactory hallucinations.

Comment. This case illustrates some of the characteristic qualities of forced thought. Such thoughts are usually very vivid, as they were with K. Especially characteristic is the mode of onset; generally they are not initiated by association, but come abruptly and without apparent purpose, just as do the muscular movements of the subsequent convulsion. The patient himself noticed this and spoke of it. This unphysiological mode of onset is usual but not invariable, as the next case will show. Forced thoughts are often accompanied by an emotion and most commonly an unpleasant one; this was noted in other cases which have been reported, and a number of Wilson's cases showed it (1). Often there is amnesia for the thoughts but this was not the case with K.

Case 2. Episodes during which jingles and rhymes would suddenly begin to run through the patient's mind, to be followed by *petit mal* seizures.

E. S., a 37 year old housewife, was studied on the Neurological Service of Dr. I. S. Wechsler at The Mount Sinai Hospital. She presented electroencephalographic evidence of a lesion in the left temporal lobe; the electroencephalographic study was made by Dr. Hans Strauss. No operation was performed.

Over a period of six months she had had two generalized convulsions, as well as episodes occurring once or more daily, which were described as follows: A "jingle, a rhyme or a proverb" would suddenly begin to run through her mind. Sometimes this seemed to be suggested by words said by others; most frequently it occurred entirely independently, without any stimulus or association. The jingle or rhyme kept repeating itself over and over again; it was always a fragment of something familiar which she tried to complete or understand, but could not. At the same time she had the feeling that things about her were distant, strange and far away; "it's like looking through the wrong end of a telescope," although things did not actually appear larger or smaller. Then her face would redden, her heart would pound and she would feel shaky and upset. The episodes terminated by her feeling, for a moment or two, that she was becoming rigid and by inability to talk or move.

The patient had amnesia for the actual jingles, rhymes and proverbs. She had no olfactory or gustatory hallucinations.

Comment. In this instance is shown a variety of forced thought in which the content is always in the same general category. The occasional onset by suggestion from the words of others may mean that an attack was about to occur, and that the words heard at that moment were incorporated into the thoughts of the attack. The employment of such actual material in the content of the attack is reminiscent of the case of R.H., reported elsewhere (2). E.S. also showed the phenomenon of repetition of the same thought in a given attack, again suggesting R.H. As in the majority of cases, E.S. had amnesia for the actual thoughts and could only remember and report their general category; with E.S. the category was jingles, rhymes and proverbs; in many other instances it is "stories." No unpleasant emotion, except the feeling of strangeness, occurred in the present case.

DISCUSSION

Jackson (3) and Wilson (1) have reported whole series of cases in which lesions of the temporal lobe were manifested by various sorts of paroxysmal disturbances of thought. All of these disturbances were summed up together under the general heading of "dreamy state". They included the *déjà* phenomenon and also (Wilson's classification) states of familiarity, strangeness or unreality, and panoramic memory phenomena. The summation in one concept, the "dreamy state," of such phenomenologically divergent states as that of *déjà* and panoramic memory appears to blur what might otherwise be a somewhat clearer formulation. If we break down the "dreamy state" even into two major components, a more comprehensible view of the role of the temporal lobe in its production may result. These two major components are:

1. The *déjà* phenomenon and the feeling of strangeness.
2. Panoramic memory or fragments of it.

To derive a conception of the part played by the temporal lobe in eliciting these phenomena, the panoramic memory type of symptom may be subjected to analysis. Brickner, Rosner and Munro (2) reported two cases of verified right temporal lobe tumor, in which the aurae of seizures were the presenting to the mind, in one instance, of a certain thought and in the other, of the beginning of a certain story. It is reasonable to assume that the experiences of these two patients represent fragments of the much more inclusive experiences of Wilson's and Jackson's "panoramic memory" patients; the latter in their aurae recalled complete events and scenes from earlier days, including those of childhood. Whether the thought excited as an aura is a brief, simple one or a lengthy, complicated one, the principle underlying its excitation should be the same.

The specific eliciting of thought by a physical or physiological process such as the epileptic one appears to tell us something of the neurological foundation of thought itself (4). This fact finds its best explanation in the theory that thoughts are the consequence of the action of neurones, exactly as are the muscular movements which often constitute the more conspicuous part of the seizure. Even isolated, brief, identifiable thoughts can be so elicited, showing that although intellect is not localized as such to any particular cortical area, each individual thought has its own discrete localization in certain neurone beds.

But if thought itself is not localized to any one part of the cortex, what is it which is apparently localized in the temporal cortex, and which causes so many different things to happen to thought? Some function must reside there, a function which can influence the way in which neurones of thought behave, no matter where those neurones are located. For it would strain the imagination too greatly to believe that all the thoughts which seem familiar or strange, or which are excited by the epileptic process, are thoughts whose neurones are in the temporal cortex. Hence we are obliged to suppose that the intellectual phenomena under discussion represent neurone beds which may lie anywhere in the cortex, but which are caused to behave in a certain manner by something which happens in the temporal cortex. We know of no cases in which such symptoms have been reported as resulting from disturbances elsewhere in the brain.

The suggestion emerging from these observations is that one or both temporal cortices has the capacity to stimulate neurones of intellect into action, no matter where in the brain they may lie.

We would stress that this suggestion is not an explanation of the entire "dreamy state". It does not account for either the *déjà* phenomenon or the feeling of strangeness, except in a very general way—that these states too represent something that happens to neurones of thought in various parts of the brain; what that something is, we do not know, but the evidence indicates again, that it is a process of some kind which starts in the temporal cortex, and influences the cortex everywhere and anywhere. Obviously it is not identical with the apparently more basic process of intellectual excitation we have just referred to. It is of interest that the process which creates the feeling of familiarity can be attached not alone to an actual experience, as it usually is, but also to a forced thought, as it was with K.

The reality of influence upon thinking, exerted from a remote cortical area has been shown by an observation recently reported (5). The observation was that repetitive speech could be elicited by electrical stimulation of an area in the frontal cortex far from any known part of the speech zone.

Repetitiveness is a general process, which applies to any function of the cortex. In the case just alluded to, it was concerned with speech. In that instance it was elicited from an area in the left frontal lobe. But repetitiveness can be seen in its relation to functions other than speech; its application to auditory concepts was observed in the case of R.H. (2); to thought itself, in the repetition of jingles etc., experienced by E.S., who is reported in this communication. In both of these instances, repetitiveness was elicited from the temporal lobe. Thus we can discern still another type of influence upon distant neurones of thought which can be initiated in the temporal lobe. However, the capacity to cause distant neurones to act repetitively is not limited to the temporal lobe.

Corroboration of an influence upon distant neurones from the temporal cortex is found in the visual hallucinations which may result from temporal lobe lesions. The explanation that such hallucinations are caused by stimulation of the intra-temporal optic radiations has never been satisfactory, because all evidences suggest that such complex states arise in the cortex itself. But if we postulate a spread of excitation from the temporal to the occipital cortex, we have an explanation of the visual hallucinations which is compatible with our general concept of cortical function.

Wilson suggested that the phenomena of the "dreamy state" as well as the visual hallucinations resulted from the spread of the epileptic impulse itself from the temporal cortex. But this does not really account for the excitation of distant thought neurones by something which happens in the temporal cortex only; if it did, the same result would have to be expected from a discharge spreading from any focus anywhere. Yet temporal lobe lesions characteristically do result specifically in the activation of thoughts. Therefore we are still driven to the postulation that the temporal cortex contains starting points for stimuli which specifically activate distant neurones of thought. It is not impossible that

the thing which spreads from the temporal cortex under these pathological circumstances is the epileptic process and not the normal nerve impulses. This would not change our meaning, however, because it would nonetheless reveal the presence of anatomical pathways along which nothing but the nerve impulse could pass, under normal conditions.

The temporal lobe is a place where one might expect to find a central station for the influencing of thought, if such a station existed. This is so because we already know it to be a central station of intellectual processes, in its role as a synthesizing agent for simpler engrammes arising in the occipital and parietal (and also the temporal auditory) receiving stations.

The evidence is not conclusive as to whether or not the functions we attribute to the temporal cortex are limited to the dominant lobe.

SUMMARY

1. Two cases are described in which "forced thought" was a manifestation of a temporal lobe lesion. (In one instance, the lesion was proved at autopsy; in the other only electroencephalographic evidence was obtained.)

2. In one of the cases there was a feeling of familiarity for the forced thoughts (*déjà pensée*).

3. It is suggested that if the "dreamy state" of Wilson is broken down into some of its phenomenological components, then the meaning as well as the role of the temporal cortex in their production may become clearer. A theory of their genesis is presented, which suggests a hitherto unreported neurophysiological function of the temporal cortex.

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CEREBRAL CONCUSSION

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For many years, the nature and definition of cerebral concussion from clinical as well as pathological viewpoints have proven to be knotty problems for those concerned with the treatment of head injuries. It is only recently that some order has begun to appear in the midst of confusion.

What is the structural basis of cerebral concussion? Before one can answer this question satisfactorily one must investigate 1) the peculiarities of the brain and spinal cord together with their bony enclosures which make cerebral and, to a lesser degree, spinal concussion so common; 2) the physical factors at work in the production of these conditions and 3) the details of the abnormal tissue reactions responsible for the cerebral symptoms. In this discussion human cerebral concussion will be considered especially in terms of its most important symptom, that is, partial or complete loss of consciousness, or other derangement thereof.

In the case of the brain and spinal cord we are dealing with more or less solid viscera surrounded by a thin fluid layer, closely encased in a fairly rigid bony box. When the brain is shaken up and/or the skull is momentarily deformed by the impact of a powerful force, the brain cannot translate the force into motion, i.e., the brain cannot move away in the intracranial cavity. This seems quite obvious, especially if one compares the brain with a hollow viscus in the peritoneal cavity. Concussion of the stomach does not exist because this viscus can easily change its shape within itself or be moved about freely in the peritoneal cavity. The brain is more or less fixed and must take up the force of the shaking or blow if these are not "absorbed" by breaking of cranial bones or the intermediation of other protective agents.

In their recent, very important study of experimental cerebral concussion, Denny-Brown and Russell (1) analyse the parts played by the physical factors. They point out that there are two types of cerebral concussion: acceleration concussion, this is produced by "the stress clearly derived from the inertia of the brain when the head is accelerated from its momentum when decelerated . . . the effect produced is directly proportional to the velocity of the striking object." The essential factors in the operation of this type of trauma are the quick application of the force producing the acceleration and then the speedy cessation of the force's action. The second type, which Denny-Brown and Russell describe as "compression-concussion", is much less common and is brought about by momentary distortion of the shape of the skull, the compression being sufficient to cause fracture, mostly of the depressed type. In this connection the contribution of Scott (2) is cited. In his work on dogs, he found that when the dog's head is held in a fixed position, a blow to the skull sufficient to cause unconsciousness is accompanied by a great rise in intracranial pressure. In four animals, the average height of intracranial pressure so produced was 327 mm. of

mercury; these levels were maintained for an average of two-fifths of a second and unconsciousness lasted for an average of four and three-quarter minutes.

In both of these types of concussion, the *rate* of physical change is of paramount importance, and the effects on the brain must be of a *generalized* nature. Denny-Brown and Russell point out again that in the case of a small area of impact with penetration of the skull, the victim will not suffer from cerebral concussion even though he sustains local contusion or local laceration of the brain. In going through the skull, the force of acceleration is much reduced, and the small area of impact focalizes the effects of the injury. This is well illustrated by the case reported by Davidoff (3). A man of 36 years developed convulsive seizures when he was 31 years old. X-ray examination of the skull disclosed the presence of a .44 calibre steel bullet in his brain in the region of the splenium of the corpus callosum. The only injury to his head that the patient could recall occurred 18 years previously, when he was a soldier in the First World War. One day he was standing near a rifle range watching others engaged in target practice. He felt a brief stinging sensation in the scalp, thought nothing of it and was not further indisposed, yet apparently he had suffered a penetrating wound of the skull and a degree of laceration of the brain, without any impairment of consciousness or other immediate, serious symptoms of a cerebral nature.

Non-penetrating injuries of the skull, (i.e., those unassociated with fracture of the cranial bones) may rarely produce cerebral contusion without being accompanied by symptoms of cerebral concussion. This occurred in the case of W. F., a boy of 16 years, who was admitted to Bellevue Hospital (Neurological Service[1]) on June 2, 1938, forty-five minutes after he was struck in the left temporal region by a baseball. He was not rendered unconscious or even dazed: this was affirmed by observers at the game. Almost immediately following the accident he noticed difficulty in speech. He was able to walk home, and then was removed to the hospital. A nominal aphasia was found, together with a mild right-sided hemiparesis. The fundi and fields of vision were normal and continued to remain so. Soon after admission on June 2, 1938 a lumbar puncture revealed a pinkish cloudy fluid under a pressure of 160 mm. of water: the red blood cell count was 240. The Pandy was one plus. The total protein was 30 mg. per cent, the Wassermann reaction was negative. Cerebrospinal fluid examination was repeated on June 18, 1938. It was clear, colorless, the pressure was 120 mm. of water; 14 red blood cells were counted; the total protein was again 30 mg. per cent. The colloidal gold curve was 0000000000. X-ray examinations revealed no evidence of skull fracture. Rapid improvement set in. On June 20 he was allowed out of bed and on June 24, 1938, the date of his discharge, only very slight weakness could be found in the right lower limb. His final recovery was complete and uneventful. This boy undoubtedly sustained a cerebral contusion, yet at no time were any symptoms of concussion complained of, such as impairment of consciousness, headache and dizziness. At the time of the injury he was wearing a cap; very likely this reduced the accelerating force of the baseball and helped to focalize the effects of the injury.

[1] The writer is indebted to Dr. Foster Kennedy, director of the service, for permission to report this case.

The ultimate structural basis, i.e., the pathology of cerebral concussion has given rise to much inquiry and speculation. The matter has been complicated by the fact that injured cerebral tissues reveal a rich variety of abnormal changes, not always to be correlated with the shifting clinical pictures presented by these patients. Capillary and larger-sized hemorrhages in the brain and meninges and in the epidural, subdural and subarachnoid spaces and in the subpial tissues, venous congestion and/or cerebral edema, and a variety of degenerative and reactive changes in the neuronal and glial elements have been found in fatal cases. Increased intracranial pressure and cerebral anemia (and anoxia) have been regarded as important results of these lesions, yet a number of reliable observers have pointed out that there are not a few cases in which the cerebral lesions studied post-mortem, are not sufficient to account for the rapidly fatali course (Jefferson (4)). Indeed, in some patients dying shortly after the recept of severe head injury, no cerebral pathology is disclosed which can account for the patient's death. All this has led students of the subject to the belief that the signs of cerebral concussion (and here again the symptomatic emphasis is on partial or complete loss of consciousness, or other derangements of consciousness) are due to direct effects on cerebral neurones, of a widespread nature, induced by physical stress, which produces a paralysis of nervous function. The exact nature of these cellular changes is as yet undefined: the abnormal process may be reversible and perfect recovery of function ensue. Denny-Brown and Russell would apply the term "cerebral contusion" to injury of the vascular tissues of the brain, changes which frequently accompany concussion or as above stated may occur alone.

When one considers the unique structure and function of neurones, cells operating in highly complicated reflex circuits with far-flung processes sometimes extending many inches from the cell-base, it should occasion no surprise that such structures are so susceptible to the effects of physical stress. We need not confine our observations to cerebral tissues in studying concussion. Spinal neurones are also affected by concussive trauma. Claude and Lhermitte (5, 6) studied the effects of concussive trauma on the spinal cord in cases observed during the First World War and pointed out that the pathology in the cord was one of necrosis of nerve cells, axis cylinders and myelin sheaths; the white was much more affected than the gray matter, and the lesions were independent of vascular damage. In other words, they demonstrated a primary neuronal pathology produced by concussive trauma.

There are several other questions which arise in connection with the concept that cerebral concussion is due to the effects of physical stress on cerebral neurones. In the frequent cases of *transient concussion,* in which a brief period of unconsciousness or a dazed state are followed by complete and rapid recovery, the disordered function of the cells is quickly righted, i.e., the process is a reversible one. When unconsciousness or traumatic stupor or traumatic delirium are prolonged for hours or days, are we to regard these symptoms purely as the result of neuronal concussion as above described, or are vascular and other lesions in the supporting tissues (i.e., cerebral contusion) also playing a part in injuring the nerve cells? In a given case this question cannot be immediately

answered. However, if recovery is finally and completely attained, one *may* be correct in assuming that the state of cerebral concussion was a prolonged one, and that abnormal vascular and other extra-neuronal factors played little or no part in the production of symptoms. On the other hand, when recovery is imperfect and such sequels as persistent headache, dizziness, memory defect, inadequate concentration, irritability and change of personality occur, one may be sure that cerebral contusion has occurred. but one cannot say that *all* these symptoms are the result of cerebral contusion (i.e., effects on cerebral neurones primarily brought about by the lesions in the cerebral vascular tree and supporting structures) and that some signs pointing to defective nervous function might not represent the after-effects of the physical (concussive) stress on particular groups of nerve cells.

For purposes of clinical study, one might divide cerebral concussion then into: a) *Transient concussion*, i.e., the very common stunning or brief loss of consciousness, quickly followed by complete recovery; b) *Prolonged concussion*, in which unconsciousness, stupor or delirium last for hours or days, unassociated with any signs of focal brain disease or heightened intracranial pressure, and in which a gradual but finally a complete recovery is attained; c) *Fatal concussion*, in which death quickly follows receipt of a severe head injury. In these cases the abnormal changes in the brain tissues as studied by present-day methods are quite inadequate to explain the fatal outcome (there being no lesions elsewhere to explain it, either); d) *Chronic cerebral concussional effects due to repeated brain injuries:* If primary concussional effects on cerebral neurones can produce prolonged disturbance in general cerebral function and even cause death, one may ask whether repeated cerebral concussions can eventually bring about a clinical picture of chronic disease of the brain. Such a syndrome, colloquially called "punch drunkenness", has become well known in recent years in pugilists who have been "knocked out" fairly often in the course of their careers. The clinical picture is a varied one and is made up of some of the following signs: change in personality, abnormal mood swings, failure of memory and powers of concentration, impairment of judgment, intellectual deterioration, and at times silly behavior. Signs of Parkinsonism, tremor of hands and tongue, ataxic phenomena including unsteadiness of gait, exaggeration of the deep reflexes with Babinski toe sign, speech disturbances, and signs of abnormal cranial nerve function, such as diplopia and nystagmus, may also be found. The prognosis is bad. It seems highly probable that this clinical picture of diffuse degenerative disease of the brain will prove to be mainly, if not entirely, the result of the effects of concussive trauma on cerebral nerve cells.

While disturbances in the function of consciousness is the most characteristic and significant sign of human cerebral concussion, other important signs also appear in cases of severe head injury. Some of these are attributable to shock with its vaso-pressor collapse, others to disturbances in particular nerve centers. Study of different types of head injury in the human and in the experimental animal shows that the vital nerve centers of the brain stem are especially susceptible to the physical stress of concussion. This has been emphasized by

Denny-Brown and Russell in animals. They have shown that "subthreshold blows often stimulate the vago-glossopharyngeal system and in this way result in depression of cardiac, vasomotor and respiratory function for 10 to 30 seconds, occasionally longer. This is a possible explanation for the knockout blow in boxing." They also state that these particular effects are "extremely variable in degree", complicate the other features of concussion, "but emerge only as the stage of paralysis passes."

The knockout blow in boxing produces some of the most interesting types of human cerebral concussive phenomena. Jokl (7) has analysed these in his interesting monograph. He implicates not only the vago-glossopharyngeal neuronal complex but also the vestibular apparatus. He cites Sherrington (8) who says that "the knockout blow where the lower jaw conveys concussion to the otocyst, reduces in a moment a vigorous athlete to an unstrung bulk of flesh whose weight alone determines its attitude, if indeed a reactionless mass can be described as possessing attitude at all." Jokl points out that this toneless deposturing may or may not be accompanied by unconsciousness. Whether this form of collapse is mainly a peripheral labyrinthine effect or is sometimes a central medullary vestibular concussive reaction is not settled. The importance of injury to the medulla oblongata from the standpoint of pressure is emphasized by Breslauer-Shück (9). In experiments on cats and dogs, he found that slight pressure on the medulla causes unconsciousness very quickly, whereas moderate pressure on the convexity of the brain fails to bring this about.

The main reason for attempting to understand as clearly as possible the effects of injury on cerebral and spinal tissues is to improve our methods of preventing these injuries and treating them. A rational therapy can be planned only if one knows precisely with what one is dealing. In this short resumé the essential structural background of cerebral concussion and its relation to cerebral contusion are discussed.

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SUPRATENTORIAL BLOOD VESSEL TUMORS WITH CYST FORMATION

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In the monograph, "Blood Vessel Tumors of the Brain" by Cushing and Bailey (6) is found the following: "From this account, it can be seen that the list of true blood vessel tumors in the cerebrum is an exceedingly meager one. We have met with no example ourselves; Lindau believes they do not occur; and of the cases that we are inclined to accept, the histological report of all of them except that of Borchers is wanting in detail, and even in Borchers' case damaging criticism of the diagnosis might be made." This rather positive statement is modified by a footnote which reads: "In the face of all this expressed scepticism about the occurrence of the angioblastomas in the cerebral hemispheres the authors feel obliged to confess that in their series of tumors classified as meningiomas, there are three which not only have the architectural structure of the angioblastomas but which showed by Perdrau's method the rich reticular network which we have seen to be a striking characteristic of these lesions." The history and the microscopic studies of these three tumors is detailed in the Archives of Pathology (1) and again the doubt of the accuracy of the classification is expressed, and the possibility of a transition between the meningiomas and the blood vessel tumors mentioned. In his book "Meningiomas" (5) Cushing lists three more angioblastic meningiomas; in addition two other variants of the angioblastic tumors are described, one as the transitional angioblastic meningioma of which there were eleven examples, four of them cystic, and the angioblastomatous meningiomas, two spinal and two subtentorial. Of the latter the author states that they are histologically identical with the angioblastomas of the cerebellum. The very title of a paper by Wolf and Cowen, "Angioblastic Meningiomas (Supratentorial Hemangiomas)" emphasizes the difficulties of the differentiation. Six tumors are described in detail, all had dural attachments, all were considered to be transitional tumors between the meningiomas and the hemangiomas. The authors refer to the cases reported by Corten, Rochat, Barnard and Walshe, and Bailey and Bucy. Of these Rochat's case had in addition to a supratentorial hemangioma three cerebellar vascular tumors, and was a member of a family in which other cases of Lindau's Disease appeared. One must seriously question the inclusion of such a case in the meningioma group. The case reported by Häussler and Döring (8) in 1939 may, however, fall into this group although the authors call it a hemangioblastoma. The lesion was a cystic tumor attached to the dura in the parietal region. And while the authors discuss the possibility of the tumor being either a transitional angioblastic meningioma or an angioblastic meningioma they decide in favor of hemangioblastoma largely on the grounds that the tumor was cystic.

That uncertainty in the classification of a tumor may arise is readily understood. But it is unfortunate that difficulties are increased by the multiplicity

of terms used and the lack of a standard nomenclature for identical lesions. Thus hemangiomas and hemangioblastomas are used to express the same type of tumor. Moreover hemangioendothelioma is also used for the same lesion. Thus in a paper on Lindau's Disease by MacDonald (9) the cerebellar tumor is referred to in several cases as hemangioendothelioma. Nowhere is the intimate relationship of these tumors more clearly set forth than in the paper on meningiomas by Globus (7). His thesis of the development of the tumors (meningiomas) based on their phylogenetic and ontogenetic history logically explains the present

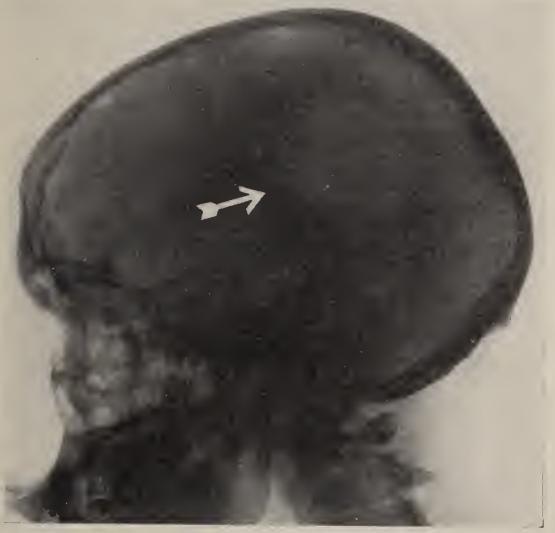

FIG. 1. Case 1. Cyst of occipital lobe filled with air

confusion and offers a solution. The final designation of a tumor whether meningioma piale or hemangioma will depend on the character of the structures which predominate. Nor has the label solely academic interest, for the life history of the tumor and the ultimate prognosis of the operated patient may be read in the microscopic picture of the lesion.

Those tumors which at the present time are labelled hemangiomas are less frequently found above the tentorium. They form an interesting group, for which reason I am reporting ten cases. From the viewpoint of gross pathology and from the picture they presented on the operating table they may be divided into three subgroups. A separate report of the histology of these and allied tumors is in preparation for subsequent publication.

The first group bears a very close resemblance to the cystic hemangiomas of the cerebellum. There were four of these cystic tumors and in three of them a mural nodule projected into the cyst. Two of these cases have previously been reported at length. Case 1 was an occipital lobe tumor (2), (fig. 1) Case 2 a left frontal lobe cyst communicating with the ventricle (3). The third case follows:

CASE REPORTS

Case 3 (Adm. 397388). In 1936 a 24 year old single woman was admitted to the neurological service of The Mount Sinai Hospital. She had been ill only seven weeks complaining of headaches, vomiting and crying spells. Her gait was unsteady, and finger-to-nose tests were carried out poorly with the left hand, which may have been due to a very slight weakness of that arm. The only other positive finding was bilateral papilledema.

A ventriculogram resolved the doubt as to whether the tumor lay above or below the tentorium. It showed a shift of the ventricles to the left. At operation a cyst containing about 20 cc. of deep yellow fluid was found 3 cm. from the surface in the right temporal lobe. The cyst wall extruded itself *in toto*; what was thought to be a mural nodule proved to be a blood clot.

The specimen was examined by Dr. Globus who reported as follows: "Sections stained with hematoxylin and eosin show a cyst wall made up primarily of numerous vessels of various sizes and with a stroma which has undergone a mild degree of hyalinization. The tissue adjacent to the cyst wall shows gliosis. The blood clot which was within the cyst shows a fragment of degenerating brain tissue. There is a probability of this being a meningioma. Here and there are islands of what appear to be foam cells. One gains the impression that we are dealing with a meningioma of the hemangiomatous type, cystic in variety into which spontaneous hemorrhage has taken place. Diagnosis: Hemangiomatous meningioma."

This case serves as a connecting link to the second group to be described in which gross hemorrhage took place into the cyst. The pathological report of meningiomas in this and the next case of this group did not militate against the inclusion of these cases.

Case 4 (Adm. 408089). A 27 year old man was transferred to this hospital from another institution in 1936. He had had severe headaches for about one year but continued to work up to two months prior to hospitalization. Then blurred vision and personality changes followed by convulsions and stupor caused him to be admitted to a hospital. He responded to treatment so that at the time he came under our observation he was dull but cooperative. His speech was thick and showed some evidence of aphasia. His handwriting was unsteady. Skilled acts were carried out poorly with the right hand. The suprapatellar reflex was more active on the right, the ankle jerk was more active on the left. A positive Babinski sign was obtained on the left. The fundi showed papilledema with hemorrhages. There was a left external rectus weakness and a right mimetic facial paresis.

At operation a cyst containing more than 50 cc. of xanthochromic fluid was found in the left premotor area two and a half centimeters from the surface. Inspection of the interior of the cyst failed to show any tumor.

Eight months after he left the hospital he was readmitted because of the return of headaches and of convulsions. Aside from a slight right hemiparesis his condition was about the same as on the first admission. Through an anterior burr hole the cyst was aspirated, 120 cc. of yellow fluid was removed and air was injected. The x-ray films showed the cyst well outlined and what appeared to be a mural nodule projecting into the cavity (fig. 2) from its superior wall. This proved to be the correct interpretation, for at operation a

vascular tumor about the size of an English walnut was found and removed from this location.

Dr. Globus reported the microscopic findings as follows: "The specimen consists of an encapsulated mass about 3 cm. in diameter. Hematoxylin and eosin stained sections of the tissue show a great number of large and small blood vessels. The vessels are congested and there are also many hemorrhagic foci in the tissues. Surrounding the vessels are streams of cells, the predominating type being fusiform in outline with large vesicular nuclei. The cells lie in a firm reticulum of connective tissue. Diagnosis: Meningioma—hemangiomatous type."

FIG. 2. Case 4. Cyst of frontal lobe after injection of air. Showing mural nodule projecting from superior wall

In spite of the fact that two of the four cases in this group are reported as meningiomas I have chosen to group them as blood vessel tumors. This I have done in view of the lack of uniformity in classification as was stated in the introduction but more cogently because they grossly resemble one another. In none of them was there a dural attachment, nor, in fact, did any one of them approach the surface of the brain. This would not, of course, rule out the possibility of a meningioma for such tumors may be found even within a ventricle, nor is there any reason why such a tumor could not arise from the pial extentions carried into the brain substance with the entering blood vessels. In three of the four cases there was a cyst in the wall of which lay a tumor, a true mural

nodule. To this extent they resemble in every respect the cystic hemangiomas of the cerebellum.

In one case, the cyst communicated with the ventricle; in two of the others, the paper-thin wall of the ventricle formed one of the walls of the cyst. The four patients were all in the third decade of life. Three of the patients are alive eight, five and five years respectively after operation, while one succumbed eight weeks after the operation. One of the survivors is incapacitated because of frequent convulsive seizures, the other two are earning their living. From the viewpoint of the contents of the cyst an indication is had of what was found in the next group. It will be remembered that one cyst wall showed microscopic evidence of hemorrhages, one cyst that communicated with the ventricle contained bloody fluid and a third cyst contained a blood clot. In the next group (cases 5–8) the cysts were completely filled with old fluid and clotted blood. In each one of the four cases it was impossible to distinguish the lesion from a spontaneous intracerebral hemorrhage until the microscopic study of the specimens had been made.

Case 5 (Adm. 409328). In 1930 a twenty-five year old unmarried woman was admitted to the hospital because of pain in the right arm of five days duration. Except for a fall in which she struck her head a few weeks prior to the onset of her complaints she had had no illness or accidents. In addition to the pain in the arm she experienced some dizziness. Three days prior to admission the patient awoke to find that her right arm was moving in a clonic manner. These attacks were repeated several times that day and the next. On the day of admission she had a convulsion which spread from the arm to involve the entire right side of the body. There was no loss of consciousness during any of the attacks.

On examination she was found to have a right hemiparesis, with increase in the deep reflexes on the right and a positive Babinski reflex on that side. There was astereognosis in the right hand and impaired position sense in the right fingers and toes. Encephalography showed the ventricles shifted to the right and the left lateral ventricle compressed from above.

At operation the gyri in the post-Rolandic area on the left were flattened and a bluish discoloration was noted through the cortex. On incising the cortex an old blood clot, estimated at over one ounce, extruded itself. A shaggy membrane which enclosed the clot was then readily dissected free from the brain substance.

The report from the laboratory by Dr. Globus was as follows: "Specimen 1. This consists of about a dozen large pieces of dark tissue which appears to be blood clot. The mass weighs 12.5 grams. Specimen 2. This consists of half a dozen pieces of pale soft tissue to which are attached small pieces of dark blood clot. The specimen weighs 6 grams. The microscopic examination of the tissue showed the first to be blood clot and the second hemangioma."

For two years after the operation the patient had occasional convulsive seizure but since that time she has been free from attacks.

Case 6 (Adm. 384730). In 1935 a 31 year old man came to the hospital complaining of headaches of five months' duration and of numbness in the left upper extremity and face for six weeks. The numbness came on in attacks lasting but a few minutes and occurring every few days. On one occasion there was involuntary movement of the fingers of the left hand. On the day of admission the numbness spread to involve the entire left side of the body and was associated with involuntary movements of the entire left arm.

On examination there was very slight weakness of the left arm and the left leg with slight increase in the deep reflexes on that side. Impairment of sensation and astereognosis were

found in the left upper extremity. The veins in the fundi were full. Encephalography showed the right lateral ventricle smaller than the left, without displacement. The subarachnoid markings on the right were poorly defined.

In spite of the absence of a ventricular shift it was thought that there was sufficient reason to carry out an exploratory craniotomy. An area of cortex in the post-Rolandic region appeared yellow, and shining through it was a bluish color. On incising the cortex there was seen a mass of blood clot and some dark fluid blood and tissue which appeared neoplastic. This tissue as reported by Dr. Globus was that "it was a vascular tumor probably of the hemangio-endothelioma type." Two days after operation the flap had to be reelevated for secondary hemorrhage. Convulsions have continued to date, but the patient is able to be employed part time.

Case 7 (Adm. 550771). In 1940 a 37 year old man was admitted to the hospital because of convulsive seizures. The onset, six days prior to admission, was marked by a feeling of numbness in the right arm which lasted about fifteen minutes. Several hours later the numb feeling returned, it spread to the face and he was observed in a convulsion limited to the right side of the body. When he regained consciousness he had a right facial weakness and his tongue deviated to the right. Prior to his entering the hospital there were two more such seizures following which his speech became thick.

There were few signs on examination. The speech was thick, there was a right facial weakness. Skilled acts were poorly carried out with the right hand and there was questionable diminution of sensation over the right face and arm. When the head was shaved for operation a small port wine nevus was seen in the scalp four centimeters from the midline in the left frontal region.

When the brain was exposed at operation a yellow area was noted in the pre-Rolandic region. When the cortex was incised old clots, fluid blood and some organized tissue which could not be identified were seen. The cavity remaining after the removal of the clots and tissue was about two and a half centimeters in diameter. Dr. Globus reported the tissue as a hemangioma.

Following discharge from the hospital the patient continues to have an occasional convulsion. A recent electroencephalogram failed to show any abnormality.

The fourth case in this group was the most recent to come under observation.

Case 8 (Adm. 473003). In 1941 a 28 year old male entered the hospital complaining of weakness of the left arm. Five weeks prior to admission a peritonsillar abscess had been incised. Following this he noted headaches and generalized weakness. Five days prior to admission he had three generalized convulsions which were said to have begun in the left face. He presented, on admission, a left hemiparesis, with hyperactive deep reflexes in the left lower extremity and depressed reflexes in the left upper extremity. There was a Babinski response on the left. Perception of pinprick was diminished over the left half of the body and face. The tongue deviated to the left. There was tenderness to percussion of the right side of the skull. The cerebrospinal fluid was under normal pressure but was deeply xanthochromic. Electroencephalography pointed to a lesion, possibly infiltrating in character, in the right tempero-parietal region. The possibility of an abscess suggested itself.

Aspiration of the right frontal region was carried out through a burr hole. The needle entered a cavity from which more than 60 cc. of blood escaped. Air was injected which visualized by x-ray examination a cavity in the right frontal lobe (fig. 3). Examination of the aspirated blood showed an island of tissue which suggested a hemangioma.

The patient improved so promptly and completely following the minor procedure that he was discharged from the hospital. A second electroencephalography gave a normal reading. In two weeks, however, he returned because of a recurrence of the convulsions and paralysis. A craniotomy was performed and the involved area exposed. The surface

of the brain appeared yellow. At a depth of two centimeters a membrane enclosing fluid blood and blood clot was uncovered. It was reported by Dr. Globus as a hemangiomatous cyst wall with hemorrhage.

The ages of the four patients in this group ranged from 25 to 37 years, which is below the age in which spontaneous intracerebral hemorrhage may be expected. The gross findings at the operating table could not, however, warrant the diagnosis of tumor. This was determined by the microscopic study of the cyst wall. In 1936 Craig and Adson (4) reported their results of craniotomy in nine cases of intracranial hemorrhage. More recently Cobb Pilcher (10) reported a similar group of eight cases. In some of the reported cases there was an antecedent history of trauma to the head, in others there was no etiological factor which could be determined in spite of histological study of the operative specimens.

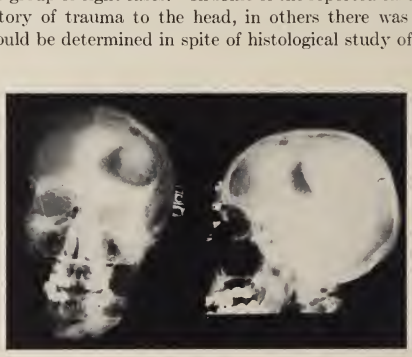

FIG. 3. Case 8. Blood clot and tumor outlined by air in cyst

The third group is made up of two cases which have in common the fact that the tumor appeared on the surface and was adherent to the overlying dura.

Case 9 (Adm. 310799). In 1930 a 39 year old man was admitted for study because of failing vision of four weeks' duration. His illness had its onset five years prior to the visual disturbance with weakness of the left side of the body, which improved after eight months bed rest. In the course of the next four years he noted attacks of numbness of the left hand and twitchings of the left side of the body. There was never any loss of consciousness during these seizures which lasted several minutes and recurred at intervals of weeks to months apart. A year prior to admission to the hospital there was a generalized seizure with loss of consciousness. There was some doubt as to the accuracy of his observation that the failing vision was of only four weeks' duration. From the time that he noted the trouble with his eyes it progressed rapidly. In two weeks time there was barely light perception in the left eye, and by the time he came under observation that eye was completely amaurotic, and vision in the right eye was reduced to counting fingers at one foot. The left pupil was fixed to light. Both fundi showed advanced papilledema with beginning optic atrophy. The other outstanding feature was astereognosis and diminished sensation on the left side without motor weakness. The cerebrospinal fluid was xanthochromic, its pressure measured 320 mm. of water.

At operation on the right side the dura was found adherent to a bluish mass in the post-Rolandic area. The mass which was cystic projected above the surface of the brain. It

was possible to brush the brain from it and to follow it into the depths where it was separated from the ventricle by paper thin tissue which was excised with the tumor. The cyst removed *in toto* approximated 4 x 1½ x 1¼ inches.

The microscopic study by Dr. Globus showed: "Fragments of tumor with narrow margins of brain tissue attached to them display numerous large channels bounded by cellular elements which arrangement and cell type suggest the structure of hemangio-endothelioma. There are numerous true giant cells. . . . Many of the smaller cells have the appearance of fibroblasts. Others form a reticular network. . . .Diagnosis: Dural hemangioma."

The flap had to be reelevated because of bleeding. The optic atrophy advanced, and the loss of vision was noted to be complete at a follow-up examination two years later.

Case 10 (Adm. 316120). A 49 year old married woman had had headaches localized over the right eye for five months and more generalized in character for three months. There had been a progressive weakness of the left arm, leg and face followed by some return of power in the leg. Her family had noted some failure of memory.

On examination she was drowsy and uncooperative. There was groping of the left hand and a grasp reflex in that hand. A left hemiparesis was present. She had bilateral papilledema.

At operation on the right side there was noted some erosion of the inner table of the skull of the right frontal bone. The dura was adherent to a tumor in the premotor area. The growth which appeared non-infiltrating extended into the brain for about one inch. The removal of the solid mass was followed by a gush of yellow fluid from a cavity about 2 x 3 inches in diameter. It was believed at first that the tumor represented a mural nodule of a gliogenous cyst. But the report by Dr. Globus was that it was a hemangioendothelioma. Three days after the operation the patient died with the signs of pneumonia. There was no post-mortem examination.

More than any of the other tumors described in this paper these tumors resemble, certainly grossly, the tumors called by Cushing angioblastic meningiomas.

SUMMARY

The ten cases viewed as a whole had tumors of blood vessel origin lying above the tentorium. All the tumors were associated with cyst formation. In four cases the cyst contained xanthochromic fluid and tumor in a localized area of the wall of the cyst. In one of the four cases the cyst communicated with the ventricle, in two others the cyst was separated from the ventricle by tissue so thin that it could be seen through. In four cases the cyst was filled with clots and old blood, and it was only on microscopic study that tumor tissue could be recognized. In two cases the tumor was adherent to the dura. One of these was a thick walled cyst which extended from the dura to the ventricle, the other tumor lay in the outer wall of the cyst.

With one exception the patients all fall into the age group between 20 and 40 years. The clinical signs were those that were to be expected from the location of the tumor. Those in the Rolandic area had convulsive seizures, either focal or generalized. The history was short and the progression was rapid in all but two of the cases. One of these patients had had headache for many years. Under observation his outstanding symptom, hemianopsia, varied from time to time. In the other patient a hemiparesis is said to have cleared up and remained absent.

Two patients died in the hospital, seven of the remaining eight are known to be alive. All but two of these are working. The survival period ranges to nine years. Five of the patients who had convulsions prior to operation have had some seizures in the postoperative course. In two of these the seizures have incapacitated them from working. In general the immediate and ultimate prognosis of these tumors is good.

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APHASIC DISORDERS OF SIGNALLING (CONSTITUTIONAL AND ACQUIRED) OCCURRING IN NAVAL SIGNALMEN

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Speech may be looked upon as a means for the expression or interchange of ideas and emotions. In accepting this rather broad conception of speech, we assume that there are modes of expression other than by words, whether as spoken or written symbols. It is indisputable that in certain circumstances various art-forms, e.g., music, painting, sculpture, the dance, can serve as methods of expressing ideas and emotions, and these may be correctly regarded as a form of speech. Furthermore under other conditions, where there has been deprivation of one or more special senses, various manoeuvers must be adopted to serve as speech. Examples can be cited in the Braille reading of the blind and the gesture-language of deaf-mutes. Then again in circumstances where secrecy is required, or where distance prevents verbal speech, other methods of communication are employed; hence the sign-talk of aborigines and the numerous methods of signalling—by drum beat, telegraphy, semaphore and so on. When speed becomes a factor of importance, we see the introduction of shorthand into the domain of speech.

Not unnaturally, investigators of aphasia have interested themselves mainly in disorders of spoken and written speech, and many of the other aspects of inter-communication have been neglected. There are, however, noteworthy contributions to the subject of the impaired musical faculties after cerebral lesions (Feuchtwanger; Ustvedt). Gross defects in drawing have been described in a case of transitory aphasia by Foster Kennedy and Wolf. Cases of "aphasia" in the deaf-mute characterized by disordered finger-talk have been published by Grasset, and by Critchley, the defect being of an apraxic nature in the former case. An aphasic defect in the assembling of leaden type upon a compositor's "stick" has also been observed (Hamilton). As far as can be determined there has been no report upon the role of Braille-reading in blind subjects who have subsequently developed focal cerebral lesions, although there is evidence that this acquisition can be impaired along with spoken speech after lesions of the left hemisphere.

Neither have there been so far any reports as to specific disorders of communication, receptive or expressive, in professional signallers who have developed focal cerebral disease with or without accompanying aphasia. The cases about to be described, are for this reason, of interest; and although they do not illustrate any clear-cut defect of signal-reading or signal-transmission (sensory or motor "asemantia," as it might be called) they do offer interesting points for discussion, and should stimulate further inquiries along the same lines.

Signalling. The traditional methods for the transmission and reception of messages across moderate or extreme distances, without the intervention of spoken speech, comprise Morse telegraphy (entailing the use of a buzzer, or some

other tapping-instrument); flashing-light signals; semaphore; and hoists of flags. Passing reference may be made to the African practice of long-distance signalling with drum-beats.

Telegraphy and flashing-light signals are both based upon the Morse alphabet of combinations of dots and dashes; the former, which is mainly an auditory method of communication, transcends all barriers of distance; the latter, a purely visual system, is limited by the range of vision, a matter of miles. Morse telegraphy, as carried out by experts, may constitute a system of speech of great complexity and refinement. The operators may learn in time to recognise one another's "touch." By the use of abbreviations, whereby single letters take the place of words, phrases or even sentences—and other devices, it is possible to transmit with speed and with facility, shades of meaning, witticisms, innuendoes, and double entendres. It is also possible by other tactile gestures to register such feelings as amusement or annoyance. All these ideas are communicable, it should be noted, at a speed greater than spoken speech, resembling in this way the sign-language of deaf-mutes.

Employing the terminology of Hughlings Jackson, we look upon a spoken phrase as the symbol of an idea, and upon written words as "symbols of symbols." A certain combination of dots and dashes come to mean something to the signaller and to "stand for" a word or phrase: in this way they might be regarded as "symbols of symbols of symbols." But as facility is obtained after many years of professional telegraphy, the Morse speech probably assumes a physiological and psychological status as lofty as that of spoken or written speech; the Morse code then ceases to "stand for" words, and becomes the direct symbol of thought.

Thus some of the older post-office telegraphists attain such ease in reading messages that they can undoubtedly "receive" far more quickly than could be transmitted by ordinary key-board methods. At least one telegraphist has stated that it would be less trouble to take in the contents of a book if only he could sit back and listen to the reading matter being transmitted telegraphically; in this way he would spare himself the more onerous task of reading the print.

Flashlight signalling is taught in the signal schools of the British Royal Navy almost to the exclusion of the "buzzer" or auditory methods of conveying singals which are within the province of the telegraphist branch. The same Morse alphabet forms the basis, but the light signals differ from telegraphy in being slower. Nothing like the speed of telegraphy either in sending or receiving is ever attained. Moreover, Naval signalmen do not devote themselves to their job so intensively as post-office telegraphists, who remain at their instruments many hours a day, and every day. Nevertheless, a certain amount of "individuality" becomes attached to the flash-light signalling of each experienced operator, and the identity of the sender can at times be recognised by an adept. Although flashlight signalling seems to be essentially a visual activity, it is questionable whether the mental image or engram is a purely visual one. The use of the hand in operating the lamp and the time-relationship of the dashes to the dots (one being three times as long-lasting as the other) introduces both kinaesthetic and auditory qualities to the problem.

Semaphore signalling is less elastic a medium than Morse telegraphy or flashlight. Its reception is a purely visual process, and the system is mainly an alphabetical one and hence relatively slow and unadaptable.

Hoists of signals are quite independent of the Morse alphabet. They comprise a series of colored flags which may represent numerals, or letters. Words are made up of combinations of letter-flags, or by special flags. In this respect they are purely visual symbols, and the processes of learning, recall, and recognition must surely depend upon mechanisms more exclusively visual than in the case of flashlight signalling.

Signal-speech differs in one particular from spoken speech in that it is almost exclusively made up of propositional components. "Inferior speech," "emotional" or "interjectional" speech are almost entirely absent from messages transmitted by Morse code, semaphore, or hoists of flags. An exception can perhaps be cited in those rare cases of very experienced telegraphists who can express emotional variations by way of their instrument (e.g., laughter, annoyance).

Education in signalling. The average young person finds no insurmountable difficulties in learning the technique of signalling, provided sufficient time is devoted to practice and supervision is adequate. In acquiring the art of Morse signalling, both with telegraph and with flashlamps, the student first masters and memorizes the alphabet and then practises sending and receiving. The speeds are then gradually increased as facility is acquired. At first, sending is found to be easier than receiving, and this usually remains the case, until the signalman has become very experienced. Later, the reverse occurs. In this case, receiving becomes an almost "passive" art requiring little or no call upon attention and but little mental effort. Sending never quite attains this same height of automatic activity, nor the same facility.

Signalling is learned far more readily by young adults and adolescents than by the elderly. It has become a practice in Signal and Telegraph Schools to accept no candidates over the age of 30, owing to a greater slowness in gaining expertise.

From time to time instructors at signal-schools are said to come across new entries who seem never to master their subject, though young in years, educated, and intelligent. It seems as though the receiving of signals, whether by ear or by the eye, remains a matter of great difficulty, so that speed is never attained. One letter seems to blend with the next and dots never seem very different from dashes. Frequently, these backward pupils are sent to the ophthalmic specialist, under the suspicion of some visual defect, though none usually is found. Just how frequently these difficult cases occur within each batch of new-entries is not known, and the impressions of different instructors vary considerably. Sometimes it is said that after many months, or even years, of perseverance, efficiency at reading Morse-signals is attained quite suddenly. It is probable, however, that most of these backward pupils will be despaired of and rejected before that time.

Although these cases of inability to learn Morse are known, they have not been specifically described. The following case record is probably the first to

draw attention to such a defect, occurring in a highly specialised manner in an intelligent young man.

Case 1. An Acting Petty Officer and Cadet Rating, aged 21, was referred for a neurological opinion on account of difficulty in learning Morse. He came of a distinguished Naval family which held an excellent health record. The patient himself was an only surviving child, healthy and normal in physical development. There was no personal or family history of any similar defects; nor of left-handedness, or stammering. He attended a South Coast Secondary School where his record, though never a brilliant one, was up to the average. His attainments were patchy: he was ahead of his classmates in chemistry and mathematics. He was at his best in geometry, for which he won a prize. English and French were easily his worst subjects, especially the latter. His difficulty did not concern the grammar, but only the spelling. Nevertheless, the spelling defects, bad as they were, did not excite any particular comment in the school. He was able to read normally, but it is uncertain whether he learned this accomplishment at the usual age, or late. He left school at 15½ in Standard IV, where he was the same age as the other boys, in order to enter the Royal Navy. He went to H.M.S. "St. Vincent" where he was immediately relegated to the Superior Grade. After a year he passed on to H.M.S. "Iron Duke" for further training and then he was sent to H.M.S. "Courageous" where he remained 2½ years. Afterwards he served in H.M.S. "Dunedin," leaving to take a course ashore in order to qualify for advancement to Leading Torpedoman. These studies were interrupted when he was recommended for a special promotion course at H.M.S. "St. Vincent" with the object of passing from the lower to the Quarterdeck. The confidential reports from the Captains had hitherto marked him out as above the average in intelligence, quickness and keenness. It was during this cadet-course that two main defects were noted, sufficiently severe and unusual to warrant medical reports. Briefly his instructors found that whereas he was adequate at all other subjects, he distinguished himself first by a proclivity for making bizarre spelling mistakes, and secondly by an inability to learn Morse signalling. The actual report of one of his officer instructors may be quoted: "He is so anxious to prove himself keen that he trips over himself. He is extremely well-mannered and polite and outwardly humble about his short-comings. He is smart in appearance, has an excellent bearing and speaks well. If integrity of character, loyalty and enthusiasm only were necessary he would be a commissioned officer; but his appalling lack of intelligence where clear and rapid thought are required—practical navigation, etc.—quite rules out that possibility. "He is an enigma. Undoubtedly keen and anxious to follow in the footsteps of his distinguished relatives, he shows knowledge and common sense in matters of seamanship. Yet in class he visibly cracks during a prolonged period of instruction and seems to lack the mental stamina required for lengthy concentration. He becomes dull and sleepy. When asked a question that requires logical thinking or is at all off the beaten track, his mind becomes a chaos of disordered thoughts, and his attempts at an answer are incoherently expressed and often rank nonsense. His confusion of thought has been manifest most particularly in his spelling, and in his reading of the Morse code made on buzzer or lamp. His spelling mistakes are not the usual ones of a normally bad speller. They are unique in that they consist of syllables transposed in a word or missed out altogether. Small words are often omitted and longer ones are deprived of their final letter. When reading the Morse code, even after eight months daily practice, he cannot sort out the dots and dashes unless it is made very slowly." When his course of instruction finished, he was recommended, not for a commission but for advancement to the rank of Warrant Officer, seamanship branch. He was at this stage transferred to the R.N.A. Hospital, Barrow Gurney, for a more complete examination in the Neuro-psychiatric Unit. There he was repeatedly seen and tested by the neuro-psychiatric specialists, Surgeon Lieutenant-Commanders D. Ross and E. W. Anderson, as well as by Surgeon Captain Desmond Curran, Consulting Psychiatrist to the Royal Navy, and by myself. Some of the points in the instructor's report could be substantiated though his comments upon general intellectual

defects could not. He proved to be, if anything, somewhat above the average in intelligence. He was very good at mental arithmetic and accurately subtracted 7 serially from 100 in 40 seconds. He could repeat nine digits forwards and at least eight digits backwards. His responses to constructive-thought tests were of superior grade. Asked the difference between "character" and "reputation" he at once replied: "The character of a person is the educated instincts of that person; reputation is the opinion others have of him." On the revised Stanford-Binet tests he also showed a superior grade of intelligence. Tests for constructive apraxia were carried out without error. He was not altogether accurate in his estimation of distances, though the defect was in no way striking. Numerous and repeated tests clearly demonstrated that there was no evidence of spatial disorientation. (This is important in view of the fact that the instructor had mentioned a tendency for him to confuse Port and Starboard while at the wheel). No defects were found in reading printed or written matter, whether silently or aloud.

Neurological and physical examination proved negative. Exhaustive tests had already been made by the ophthalmic surgeon who had been consulted at the training-establishment; no abnormalities had been revealed.

Psychiatric examination indeed revealed only three types of disability, viz:

Difficulty in spelling. This took the form of rather unusual errors. They were outstanding in frequency even when compared with the common errors of his contemporaries. A study of the "Journal" which he had to maintain each day showed that he would often omit letters or groups of letters. He would at times reverse syllables or diphthongs, e. g., he might write BRITIAN for BRITAIN. As a rule he could not correct the mistakes when they were pointed out to him; usually indeed he did not recognise that the word had been misspelled. It was also reported that on occasions he made similar reversals in speech, when excited. Thus in an extemporaneous debate he wanted to way "*writhing* in pain" but came out with "*withering* in pain." This seemed, however, to have been purely an isolated occurrence, and no spoonerisms or reversals of this sort were ever noted in the hospital.

Defects in signalling. He proved to be good at semaphore and at hoists of signal-flags. He had always had considerable difficulty with Morse signals, especially in receiving messages. Although he had originally memorized the Morse alphabet within twenty minutes, he never became able to read Morse signals with ease or rapidity despite long practice. When he was tested with flashing lights, these defects were well demonstrated. He was able to send quite accurately, though slowly. When, however, he tried to interpret a message which someone else was sending with a flash lamp, he failed utterly. He explained his difficulty by saying that he was unable to distinguish between a dot and a dash, and that one symbol seemed to run into the next, especially if the signals were given quickly. There was no difficulty in translating a group of dashes and dots into the appropriate letter, once he had read them clearly. When tested with a buzzer the same defects seemed to be apparent. This form of signalling was of course comparatively strange to him as he had been taught by way of flash-lamp signals. He obviously found great difficulty in interpreting the sounds in terms of dots and he made far more errors than did a normal control subject who was ignorant of Morse signalling. At times he was apt to omit dashes or dots from the middle or end of a signal, and thus to read: — · · · — as — · · —; or — — — as — —

Defects in ciphering. It was also discovered that despite his skill at mental arithmetic, and his good visual memory, he made odd mistakes when instructed to write down on paper numbers which were dictated to him. Thus, when told to write down "five million four hundred thousand and two" he put down: 5,40002. "Three million, four hundred and five" was written as: 30,4005. These mistakes he seemed not to recognize; nor could he correct them when they were pointed out.

The case, therefore, is one where a small number of defects stand out against a background of intellectual normality. Despite the assertions of his instructor, that the cadet was slow in cerebration and incapable of clear and rapid thought, the contrary was the case. He actually proved to be somewhat above the aver-

age in general mental attainment. The instructor's faulty judgment may have been due to a misinterpretation of the existing defects; or to failure to recognise their specificity. Or possibly he may have been misled by the presence of a mild neurotic reaction on the patient's part to the handicap of his special disability.

When the various disabilities are considered, it is found that they are actually closely comparable, and may well be regarded as aspects of one single underlying defect. Difficulty in spelling; difficulty in writing down long figures; and difficulty in recognising the component parts of a set of Morse symbols are all instances of misspelling, whether of a series of letters, of numerals, or of dots and dashes. Thus the difficulty in correctly putting on paper a number running into six or seven figures, is really an instance of misspelled ciphering, and not of acalculia. No error occurred when he was asked to write down a series of figures, or a number which did not extend beyond the tens of thousands. The real defect was revealed when he tried to translate upon paper a verbal command which ran into millions, particularly when one or more noughts came into the middle. Thus "five million and forty" would typically cause a difficulty in the correct disposition of the noughts and the commas. In this way the omission of one or more noughts, or the reversal of numeral-combinations is comparable with the omission of letters in a word or the reversal of syllables and diphthongs. Similarly an inability to guage correctly the exact number of dashes or dots in a given set, or to differentiate between the one and the other, is analogous to misspelling in Morse, as shown when he was asked to transcribe upon paper exactly what it was he thought he heard when listening to a telegraphic buzzer.

In many normal persons, minor degrees of this type of defect may exist, but they can usually be recognised and corrected by the person concerned, and with training he soon overcomes the difficulties. Thus many people would hesitate when ordered to transcribe such a sum as "five million and forty" and be a little doubtful where exactly the figure "four" should be placed among the series of noughts. The difficulty should not be an insuperable one, however, and with a little practice, the task should become an easy one.

Still more relevant is the difficulty which every beginner notices in distinguishing dots from dashes, and in determining where one letter-combination ends and the next one begins. This almost spatial defect is of course bound up with the effort to recall the meaning of each symbolic combination, a task which may lag behind the rate of sending. He is still in the stage of regarding telegraphed speech as something which is built up of numerous small units, namely individual letters. When light-signals are employed, it is almost as though the dots were longer and the dashes were shorter than they should be, owing to a sort of "halation" effect which is mental rather than visual.

This difficulty in passing rapidly from one symbol to the next, recognising quickly its visual or acoustic nature, and then promptly interpreting its meaning, is reminiscent of the difficulty which may be experienced by one, by no means ignorant of a language, in listening to a discourse in a foreign tongue. The isolated words are all familiar, but preoccupation with the need for accurate

interpretation of each word in turn may slow up the process of interpretation of the phrases or sentence as a whole. The listener has not yet passed the stage of regarding the isolated word as the unit of speech.

Normal individuals learning Morse code or a foreign tongue surmount these difficulties, however, as they gain expertise. In Jackson's terminology the activity may be said to pass from a highly voluntary to a less voluntary and more automatic one, and conscious effort at serial interpretation, symbol by symbol, is overcome. When the "proposition" and not the word, far less the letter, is recognised as the unit of speech, then efficiency is attained, in linguistics, signalling, and telegraphy alike.

It is possible that certain personality-traits might interfere with this advance from a labored voluntary interpretation of one symbol after another into a facile recognition of a symbol or set of symbols as a whole. An ideational inertia may cause the subject to occupy himself exclusively with the meaning of the first symbol, and so by a process of perseveration, the other symbols become blocked. Such might be the explanation in part of the difficulty experienced by the elderly and the arteriosclerotic individual in learning new languages or Morse telegraphy. In other cases, an obsessional preoccupation with the visual or auditory image of the symbols may hold up the ready passage of attention from one symbol in the next.

In the patient described there was no evidence whatever that either of these psychological mechanisms were at work.

The "spatial" characteristics of the Morse symbology raises the question whether the defect in the patient concerned might not be due to some innate disorder of spatial orientation, whether of a visual nature (visual disorientation) or of a personal character (disorder of the body-schema). This possibility seems to be supported by the instructor's statement that he was apt to confuse port and starboard and to be "hopeless upon the Bridge."

It can be said that no such defect could be demonstrated, either in external or internal relationships. A large number of tests, both simple and elaborate, were devised to check up his left-right orientation and he was found to pass them without a single error. On scrutinizing his story, it proved that the instructor's impression was an erroneous one based upon a single mistake upon the Bridge, when the patient misheard the orders given him.

Although he was found to be inaccurate at times in his estimation of size and distance, especially when the dimensions concerned were great, the errors were not such as to distinguish the patient from the great majority of normal persons.

The possibility, too, that this particular defect was bound up with some psychomotor disability such as a constructive apraxia, was rapidly disproved by appropriate testing.

The case in question approximates most closely the congenital dyslexias or instances of congenital word-blindness. The patient differed however in that he showed an even more specialized form of visual imperception, for he could read correctly and easily all written and printed words. That some degree of dyslexia existed is suggested by the unusual spelling-mistakes which he did not

recognise when confronted with them. One is clearly dealing with a type of symbolic dysgnosia or imperception, comparable though not identical with congenital word blindness. The case therefore seems to belong to the larger group of congenital dysphasias. The defect is mainly a receptive one, for misspellings are attributable to imperfect visual recognition, rather than to a motor type of dysgraphia. His verbal speech is intact, despite the isolated instance when under emotional stress he said "withering" for "writhing."

The occasional reversals of letters in his misspelled words; the imagined confusion of port-starboard relationships; the occurrence at least once of a reversal in his spoken speech; these are the only suggestive features which are reminiscent of Orton's views on the pathogenesis of congenital wordblindness. Further scrutiny discounts this suggestion, however, for it can be said that 1) there existed no difficulty in reading print; 2) port-starboard confusion actually did not exist; 3) the patient was right-handed and came of right-handed stock; 4) no reversals of individual letters occurred; and that 5) the reversal of spoken speech was noted only once. In the light of our present knowledge of the congenital dyslexias, and of this case in particular, it would obviously be unsafe to speculate as to any possible incoordination between the activities of the right and left hemispheres in the visual aspects of speech.

There is some similarity between this case of "signal-aphasia" and certain varieties of receptive amusia. Flash-signals represent in the visual sphere a sort of melody or rhythm, which can be recognised in buzzer-signals just as in the rhythm of certain kinds of music. Although it must be rare for a patient to lose, as the result of a cerebral lesion, all traces of emotional appreciation of crude rhythmic music, nevertheless it is not unlikely that the higher, aesthetic and more intellectual understanding of tympany may be impaired as part of an amusia. Kleist described cases of this sort under the title "pure melody deafness," which he defines as a lack of appreciation of intervals in their rhythmic structure as melodies. This defect which he associates with a lesion of Brodmann's field 22 is in many ways comparable with the defect in signalling just described.

From the point of view of recruitment, pre-selection and vocational tests, it might be important to determine how these signal-aphasics might be detected quite early in their Naval training. Unfortunately, there appears to be as yet, no satisfactory means of doing so, though investigations to this end are worth while along such suggestive lines of inquiry as: consistency or inconsistency in educational attainment; proclivity towards unusual errors in spelling; left-right disorientation; incongruity between handedness and eye-edness; unusual difficulty in comprehending spoken foreign languages; and the existence of musical rhythm-deafness.

Acquired defects in the reception or transmission of signals. It would not be surprising to find that in cases of aphasia occurring in signalmen, the specialized profession activities would likewise become involved. This idea is supported by the existence of specific constitutional difficulties in signal-learning, as illustrated by the foregoing case. Whether, in the acquired cases, the ability to transmit

and to receive signals would be lost early or late in the development of the aphasia, is not known. Neither is it known whether a defect in signalling can exist in pure form, that is, independent of any impairment in the execution or understanding of spoken and printed speech. The problem is comparable with that of aphasia in polyglots, and we are already aware that Pitre's axiom upon this subject—that the later acquired language suffers most—is an over-simple generalization, often contradicted by the facts.

The following case report, although unsatisfactory in that it concerns a global dementia, nevertheless suggests that signal-transmission can be impaired in the absence of verbal aphasia, and as part of a motor apraxia.

Case 2. Signalman, Royal Fleet Reserve, aged 39 (12 years service), suddenly noticed weakness and dysesthesia in his right foot lasting about 15 minutes in all. Recovery was complete and maintained for the next five months, until one morning he complained of the same trouble in the right hand. The next day the pins and needles had gone from the hand but had involved the right foot. He continued with his duties and the symptoms cleared up within three weeks. Three months later the same symptoms recurred and for ten minutes there was a difficulty in "getting his words out." Again his symptoms cleared up and a fortnight later he was admitted to the R.N.A. Hospital, Barrow Gurney. At this time his only complaint was slight headache, and he denied any affection of the extremities or of the speech. The report sent with him by the medical officer at his signal station indicated, however, that for three months he had been showing signs of increasing mental deterioration. It also stated that in the last two of his attacks, consciousness had been lost for a short while.

Examination at the time of admission to the hospital revealed some weakness of the right side of the face and tongue, but no trace of paresis in the arms and legs though his hand and finger movements were clumsy. The pupils were unequal and irregular, the left one being inactive and the right one sluggish to light-stimulation. All his tendon reflexes were brisk but equal on both sides of the body; both plantar responses were extensor in type. His memory proved to be much impaired. He gave the details of his history in a muddled fashion; his cerebration was slowed. Insight was defective and there were evidences of euphoria. *Speech* was slow, hesitating and dysarthric, but at no time did he misuse a word or fail to bring out the word he desired. His handwriting was executed in a labored manner but there was no real agraphia.

Morse-signalling. When asked to transmit the Morse alphabet first with his right and then with his left hand, it was apparent both subjectively and objectively that he was much more efficient with the left. With the right hand, his signalling was slow, hesitant, and irregular, and the dashes and dots were not clearly differentiated.

Examination of the cerebrospinal fluid revealed six cells; protein 40 mg. per cent; increased globulin; Wassermann reaction, positive; Lange, 5555553210.

This patient was probably suffering from a Lissauer's type of general paralysis with focal syphilitic vascular lesions superimposed upon the diffusely spread cerebral disease process. Although there was a history of a transient aphasic disturbance, there was no evidence, while he was in the hospital, of any speech affection other than a dysarthria. A difficulty in the transmission of Morse signals was clearly demonstrable, though this aspect of the case was not studied fully. The fact that this defect was of an executive nature, and that it affected the right hand only, suggests strongly an apraxic disorder. This belief is supported by the observation that he was clumsy and maladroit in such activities as fastening his pajama-jacket.

The third case is of a different type, and is of interest in that the defect in signalling which was present was of the receptive (agnostic) variety rather than executive (apraxic); it was associated with a very clear-cut visual type of aphasia; and the signalling defect was far less intense than was the disordered impairment of printed speech. The third case shares with the second the same difficulty in correlating the clinical evidence with an isolated cerebral focus of disease.

Case 3. Chief Yeoman of Signals (Pensioner), aged 57. This patient had entered the Service at the age of 15 and served for twenty-four years in the signal branch in which he attained the highest possible rating. On going out, he became a customs official until his recall to the colors in August 1939. His health had been excellent despite service in the China and West African Stations. The family history was negative, except that a brother had died from epileptic fits in his fifties. He was in excellent health, working at a signal-station, until September 1940 when he accidentally tripped and fell down a flight of stairs in the black-out. He received no direct injuries but was generally "shaken-up." He returned to duty the next day, and did not report the accident. One week later, he began to notice some trouble with his vision. He frequently imagined he saw a shadow moving somewhere to his right but when he directed his gaze in that direction he would find that there was actually nothing there. A little later he remarked that he would have to turn his head well to the right in order to see objects clearly on that side. At about the same time he discovered that he was unable to read; although he could see the printed words distinctly he could not understand their meaning at all. In the same way, although he was able to write, he could not read what he had written, except from memory. After some time he lost his difficulty in seeing to the right, but there followed a similar defect in seeing objects to the left. The difficulty in reading improved a little, so that after some delay he might ultimately arrive at the meaning of the words, but he still experienced a considerable impairment in this direction. He reported these symptoms to a medical officer who discovered a left-sided hemianopia together with a well-marked dyslexia. He was admitted to R. N. Hospital, Chatham, where these same features were confirmed, and later he was transferred to R.N.A. Hospital, Barrow Gurney.

Examination revealed a very intelligent elderly man with signs of a moderate arteriosclerosis. His radial and brachial arteries were palpable, and there was obvious though not advanced retinal vascular changes. Blood pressure was 185 systolic and 105 diastolic; heart rate was 60 per minute with occasional missed beats. Second aortic sound increased. Electrocardiogram normal.

Neurological examination showed no disorder of motor or sensory function. All tendon reflexes were present and equal; abdominal responses were obtained; plantar stimulation evoked a flexor response on each side. There was a left-sided homonymous hemianopia sparing the fixation point. The blind-spot was not enlarged. No scotomata were present. Visual acuity 6/6; 6/6 (with glasses): no defect of color vision by Ichihara's tests.

Electroencephalogram: no abnormality in any area. Wassermann reaction, negative. Cerebrospinal fluid: initial pressure, 23 mm. of water. Radiogram of skull, normal.

Speech: his spontaneous speech was correct, fluent and well articulated. There was no defect in naming objects. The only unusual feature was a tendency to misname colors, although color blindness did not exist. He understood fully and easily all that was said to him and he could carry out commands without the slightest trouble.

There was a very obvious difficulty in reading, although he had apparently improved a great deal in this respect before admission to Barrow Gurney. He would read aloud accurately, but slowly and with hesitation. Now and then he would make a particularly long pause but ultimately he would arrive at the correct rendering. When questioned as to his difficulty he replied: "I can see the words quite clearly, but I can only get the words out if I spell the first letter through from the beginning of the alphabet." Thus he hesitated for a long time before the word "five" and eventually he got it by saying to himself: "A,

B, C . . . D, E, F . . five." Small and large print were equally difficult and it made no difference if he read a word at a time, viewed through a small aperture in a sheet of paper.

He wrote fluently and neatly, with but few misspellings. The character of his handwriting is said not to have changed. Shown a specimen of his own script written some days previously he recognised it as his own, and read it correctly though slowly, just as in the case of print.

When shown pictures in an illustrated magazine, he recognised them as a whole and he could also identify the various details. It was very doubtful, however, whether he was aware of the ultimate significance, or the "point" of a picture. Thus he did not seem to be able at once to realize the difference between a photograph and a comic drawing. It was very obvious that he did not appreciate the point of the joke in a humorous drawing unless he could read the legend.

His power of map-reading was defective. Thus shown a chart of the Mediterranean, he picked out Turkey in the top right-hand corner, but nothing else. Later he said that Malta was "somewhere in the neighbourhood" but when asked to point out its situation he put his finger in the middle of Greece. Shown a map of the British Isles, he hesitatingly indicated the position of Edinburgh, his home-town, but located Glasgow only a mile or two to the west.

His powers of calculation, of retaining digits and of comprehending the meaning of proverbs were all fairly good.

Recognition of naval signs and signals. (a) *Ensigns.* He was fairly good at identifying the various national flags, though he confused those of Norway and Sweden. He did not recognise the ensign of the U.S.S.R., which he called Turkey, or of Spain. He may have been correct, however, when he explained that these two flags were "since his time."

(b) *Ships' lights.* He was fairly good at recognising the meaning of conventional arrangements of ships lights, though he made several errors. Thus he did not know the sign for a ship with two or more vessels in tow, though he knew the sign for a ship towing one vessel. He did not distinguish promptly the elementary distinction between the signals—for a "vessel at anchor" and a "vessel under way." He recognised neither the "dredger sign" nor the "pilot sign."

(c) *Hoists of signal-flags.* He picked out the numerical and alphabetical flags, both in series and individually. He failed, however, to recognise a number of common symbols, such as the "aeroplane;" "affirmative;" "blue affirmative;" "aircraft carrier;" "negative;" and "battle cruiser" flags. He recognised more of the pendants but not the substitutes, until prompted. He identified the "answering pendant" but not the "interrogative." He completely failed to read "1212" or "Hannah" though both these symbols are textbook hoists which every signalman learns early in training.

(d) He identified at once the flags flown by an Admiral, a Commodore and the Admiralty.

(e) *Semaphore signals* were imperfectly read, only in that he frequently failed to see the right hand arm of the signaller on account of his hemianopia.

(f) *Flashlight Morse signals.* He was able with fair accuracy to interpret and write down a message flashed to him at a moderate speed (10 words per minute). When he was allowed to call out the interpretation (instead of writing it down) he improved still further.

(g) *Tapping Morse signals* were accurately and quickly interpreted.

(h) He was able to transmit Morse signals, both by flashlight and by tapping, with average speed and with accuracy.

In this case there developed, after one or probably more than one vascular lesion, a left-sided hemianopia, as well as various agnostic defects concerned with the visual components of speech. These latter comprised chiefly: 1) An alexia, which later improved leaving a persisting difficulty and delay in the interpretation of written and printed symbols; 2) A defective appreciation of the ultimate significance of pictures, especially those which were impressionistic rather than

representational; 3) Impaired recognition of flag-symbols which should have been familiar by reason of his long professional contact with them; 4) A minor degree of visuo-spatial disorientation, as shown by difficulties in map-reading.

These defects are enumerated in their approximate order of severity.

In contrast with these visuo-agnostic difficulties, his ability to interpret such a highly artificial system of speech substitutes as Morse flashlight signalling, was practically intact. It might have been imagined, especially in the light of Pitre's "law of regression," that such an achievement—elaborate in its nature, late in acquisition, subservient to verbal and printed speech—would have suffered more than verbalization after a cerebral lesion of such a type. An "alexia for Morse signals" might well have occurred, greater in intensity than the "litteral alexia."

This particular case record is of interest therefore. It suggests that both on physiological and anatomical grounds, speech and signals are not identically represented in the cortex. There is a resemblance in this way to the faculties of music and speech, for a single lesion if large enough may ablate both accomplishments, whereas a small one may interfere with one or the other singly.

As mentioned earlier, the Morse system, even when learned and practised by purely visual methods, cannot be regarded as exclusively a visuo-psychic process. The assembling of dots and dashes in various combinations, with a strict ruling as to the relationships of a dot to a dash, entails both spatial and auditory mechanisms. This is further shown by the rigid conventions as to the length of interval between successive letters and between successive words. Furthermore when one recalls that in sending messages on a flash-lamp, the beam is regulated by rhythmic movements of the hand, it is clear that a sensori-motor or kinaesthetic element also takes part.

Hence a purely visuo-agnostic defect such as a litteral alexia need not necessarily imply an "alexia" for such a complicated faculty as that of Morse signalling.

The recognition of signal hoists of flags is an entirely different matter, lying entirely within the visual sphere. It would not be surprising therefore to find it suffering *pari passu* with a defective comprehension of pictures and of printed symbols, as indeed was the case in this patient.

It is unfortunate that this patient in no way helps to establish the morbid anatomy of the condition. At least two lesions must have been present, one in either hemisphere. The history suggests that a lesion of the left optic radiations was followed by a right-sided homonymous hemianopia. This proved a transient defect, however, and was later followed by a hemianopia to the opposite side. Which of these two lesions was associated with the litteral alexia, and with the impairment of code-flag reading, cannot be ascertained. Nor can it be gainsayed that in this particular patient, bilaterality of lesions may have been responsible for such signal-defects as existed. The association of alexia with hemianopia suggests the characteristic localization of a lesion within—or deep to—the angular gyrus. In this case, however, there is yet another point of interest in that the hemianopia was left-sided suggesting that the larger and more permanent lesion was in the right hemisphere.

Such clinical arguments as can be adduced in this case suggest that the lesions are both, or all, located within the visual or visuo-psychic areas of the two hemispheres, (angular gyrus, optic radiations). There is no direct evidence that any lesions exist outside these zones, and this point may perhaps be correlated with the intactness of Morse-signalling, which as has already been suggested, is not a purely visual performance.

It is unfortunate that the electroencephalogram did not throw any light upon the clinico-anatomical problem, in that it failed to reveal any abnormality whatever.

SUMMARY AND CONCLUSIONS

1. Three cases are reported, illustrating the association of defects in signalling with impairment of speech.

2. The first case seems to be one of a specific disability in reading Morse-signals in an otherwise intelligent subject. That this disability was probably allied to a congenital word-blindness is suggested by the patient's proclivity to unusual errors in spelling.

3. The second case was one of general paralysis complicated by focal syphilitic vascular lesions. The most important of these seemed to be situated within or near the left frontal lobe, causing transient weakness of the right arm or leg, and on one occasion, a transient motor aphasia. A difficulty in executing Morse-signals was demonstrable at a stage when no aphasia and no paresis existed, and must be regarded here as an apraxic manifestation.

4. The third case concerned a mild arteriopath who, after two vascular lesions, developed a partial alexia and a left-sided hemianopia. Although he was imperfect in his ability to interpret hoists of signal-flags, he could read Morse flashlight signals with accuracy and speed. His powers of reading Morse contrasted very much with his obvious difficulty in reading print or script.

Acknowledgment: For permission to quote the above cases I beg to acknowledge the kindness of the Surgeon Rear-Admiral, R.N.A. Hospital, Barrow Gurney.

PROGNOSIS AFTER ENCEPHALOPATHY IN INFANCY

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Injuries of the central nervous system in children, whether traumatic, infectious, or toxic, are a major problem in any hospital which draws its patients from a large area. The immediate medical problems are met with reasonable promptness and efficiency. If the results of treatment are disappointing doctors follow their patients and labor over the problems presented by mental defect, convulsions or paralysis. If, on the other hand, none of these sequelae appear they are apt to lose sight of children. Furthermore we all know that many children suffer injuries to the nervous system which are not called to medical attention or, worse still, are not viewed seriously by doctors.

In every psychiatric clinic the question of injury or disease of the brain arises at intervals. The parents may bring these children to the clinic long after the acute episode and offer suggestions rather than proof of cerebral damage. This group is not composed primarily of individuals with epilepsy, mental defect or paralysis. On the whole it is not even composed of children whose names appear on hospital records under the headings of encephalitis, meningitis, subdural hematoma, lead poisoning or the like. In fact, many of these children have no record of medical supervision for acute involvement of the nervous system. The diagnosis may be a retrospective one based on a careful history which shows changes of relationships to playmates and school or to members of the family, after accident or illness.

We doubt whether any attempt at statistical arrangement of available material is possible and we certainly have no basis for discussion of cases on a numerical basis since the hospital doctors report a considerable number of recoveries and the guidance clinics learn, for excellent reasons, to distrust the validity of the usual medical and surgical criteria of recovery. On the other hand, retrospective diagnoses may be equally unconvincing in certain cases to physicians who supervised acute illnesses and saw no signs of encephalopathy.

In this paper we wish to discuss the difficulties which face the doctors and their associates in dealing with children who are seen during the acute phase of cerebral disease, or during the course of diseases which frequently have cerebral manifestations. In order to bring out certain points, we have selected two young children who came under the care of this hospital, during the acute phase of encephalopathy. Each left the continuous supervision of the hospital and was brought to our attention after a lapse of time for difficulties of the type seen in guidance clinics. The serial appraisals of these children at intervals of years indicate the complexity of the problem of encephalopathies of children.

In these two cases there were no gross errors in diagnosis and treatment. Our failure lay in the field of prognosis and supervision. We failed to estab-

lish adequate criteria of recovery and it is this phase of medical care which we wish to discuss. Recovery, in the young adult, can be assumed, as soon as all medically recognizable signs of disease have disappeared, if the patient takes up his activities where he left off with undiminished energy, stamina and enjoyment and is recognised as competent by his associates. He and his doctor rejoice in the fact that he is "as good as ever." Elderly people are less exacting and expect to accept moderate limitations. Only if senility is obviously accelerated do they complain.

The child, however, needs far more than restitution to an achieved level. Recovery, as so defined, may be paraphrased as "arrested development." He must progress at his expected rate, he must make up lost ground and then move on with contemporaries who have outstripped him. The difficulties of prediction of growth and development are of course well known. We need to have a reasonably clear idea that the child, before the illness or injury, was a predictable unit and we need to follow the course of development afterwards in order to judge the adequacy of progress along the predicted curve.

It is by no means an easy matter to establish the psychological status of a child who is brought to a hospital with acute disease involving the central nervous system. To the family and often to the doctor the previous history seems almost irrelevant. However, it is relatively easy to collect information about growth and development before discharge from the hospital and much information is reasonably contemporaneous and undistorted. On the basis of the history it is possible to set up a curve of predicted development for the child and to plot against it the actual progress.

The first landmark is the point where parents and doctors and teachers begin to talk about apparent restitution to the level achieved before the illness or accident. There is every reason to rejoice when this landmark is reached but also there is need of discussion as to the significance of the event. The progress from then on must be reviewed critically. It seems to us that some children are emotionally disturbed by the pressure imposed by the increasing demands on stationary or slowly increasing intellectual capital. It is possible that very complicated abnormalities of behavior may be the result of pressures which are imposed because no adequate appraisal has been made.

The problems which arise from encephalopathies sometimes are misunderstood because of over-simplification of terminology. We use the terms post-encephalitic and post-traumatic. The implication is that the structural changes are over when the original acute episode has subsided. Certainly there is abundant evidence that changes can take place over many years. Gross or subtle disturbances of growth of brain tissue, may complicate the picture.

Time, often measured in years, is needed before durable prognoses are possible.

The first case is one of known lead poisoning. The general impression that exists in medical circles is that lead poisoning in children is relatively common and that certain of these children have encephalopathy which is characterized in its acute phase by gross edema which causes outspoken signs. Certainly

many cases follow this pattern. We see and recognize many cases of lead poisoning and our pediatric staff is, I imagine, fully as sensitive about the disease as any. It is recognized by most physicians that lead is a cumulative poison and that its excretion may be very slow. It is not, however, common knowledge, that it can form a continuing threat for a considerable series of years after ingestion. Neither is it well known that cerebral function can be impaired without outspoken signs of active encephalopathy.

CASE REPORTS

Case 1. Lead poisoning; polyneuritis; encephalopathy. This child, whose first outpatient visit was in 1927 at $2\frac{5}{12}$ years, was seen in the Out-patient Department at irregular intervals over a period of three years for occasional vomiting with or without abdominal cramps and finally for muscle weakness before the nature of the disorder was recognized. The failure of diagnosis was partly due to irregular maintenance of contact by the mother, but essentially it was the result of confused referral and counter-referral in a busy outpatient department. In mitigation it is proper to record refusal of the family to accept hospitalization early in the course of the disorder.

Finally at $5\frac{5}{12}$ years she was admitted with a diagnosis of polyneuritis due to lead. The history was then reviewed and there seemed to be no question that the child had eaten paint in important quantities early in childhood although she was not doing so at the time of entrance. The chemical and x-ray study completely proved the diagnosis. The child was carefully observed at this time, not only as a case of polyneuritis, but as a child who might be a victim of encephalopathy. We watched her first, of course, as a patient with physical disabilities.

The polyneuritis interferred with performance and the long history of disability made everyone tolerant. Even so the psychological evidence was somewhat disturbing. She was pleasant and gave the general impression of intelligence. This impression was supported by a Stanford-Binet rating of 107. However, she had definite difficulty in appreciation of spatial relationships, she could not copy a square (fourth year test) and she had more than average difficulty in copying letters.

The nursery school teacher, who had a background of nursing training, as well as adequate educational experience, also expressed some anxiety. Her notes included statements such as the following.

"It does not seem to me that this child plays normally for her age," . . . "not constructive nor imaginative in use of play material," . . . "she needs a great deal of guidance," . . . "More and more it seems to me that mere presentation of material with slight suggestion is not enough."

In spite of these reservations we all agreed that she did very well for a child who had been ill for years and who was handicapped by neuritis. From the medical point of view the excretion of lead proceeded in what we thought was a fairly predictable way. She had one severe recurrence of neuritis after infection and medical efforts were focussed on slowing down the release of lead. At $6\frac{1}{2}$ years she was still having difficulty with the formation of letters and figures, but no urgent anxiety was felt.

In December 1932, at $7\frac{1}{2}$ years, she was given a clean bill of health in the out-patient department on the basis of uninterrupted activity and the statement of the mother that she was doing satisfactory work in the second grade in school. X-ray examination showed traces, but only traces, of lead in the bones at that time. The record notes that she had passed through two severe upper respiratory infections without any signs of recurrent weakness. In 1935 all lead had left the bones by x-ray examination.

In 1936 when the child was $10\frac{9}{12}$ years old, we came in contact with her again. Quite by chance one of the school supervisors, who was at the hospital on other business, spoke of the difficulties of the child in the third and fourth grades.

The family agreed to reappraisal in the wards at this time. Again gross neurological study was essentially negative. There was slight flattening of one side of the face, but nothing to suggest serious changes in the nervous system. A pneumoencephalogram failed to reveal any evidence of structural change. The chemical studies, which were carried out with every precaution, indicated important quantities of lead in the blood and cerebrospinal fluid. These readings were made at the Massachusetts Institute of Technology and were interpreted as showing continuous excretion of lead, though in diminishing amounts. The spectroscopic method was used.

The psychological review was more significant than the physical examination. Conference with the school authorities revealed that after two years in the third grade the child was baffled by the work of the fourth grade. She was becoming a problem from the behavior point of view in school, though at home she was cheerful and helpful. On testing by the Stanford-Binet she showed a wide scatter from a basal year of six (she failed repetition of 5 digits), to one test passed at fourteen level. The intelligence rating was 92. The child could write easily but drawings showed poor orientation. She still gave an impression of adequacy, but the school work was not of passing grade. Test results were confirmed by a trial of teaching during her hospital stay. Our evidence was discussed with school authorities and our conclusions that the child was suffering from lead encephalopathy were accepted. A plan involving many concessions was put into operation. The behavior at school promptly improved.

At 15 years the girl is in the eighth grade. She is cheerful, socially competent and attractive. Her brother, two years older, is in his final year of high school. No physical signs of cerebral damage can be elicited. The blood still shows about four times as much lead as that found in the blood of most persons used as controls and these controls come from people exposed to city hazards. This is not the place to argue as to the significance of the chemical findings. However, it is obvious that the child still is regarded, by qualified chemists, as a carrier of an unusually high amount of circulating lead. She is, of course, being watched at intervals.

In this case several causes of chagrin are obvious. First, a hospital staff which is periodically reminded of lead poisoning failed to function at the start. This is regrettable, but significant. Second, a child known to have had lead poisoning was discharged from supervision on the basis of x-ray evidence. This apparently false criterion of cure does not involve any culpable error since people thoroughly familiar with plumbism do not know better. The psychological evidence indicated the existence of encephalopathy. Emotional disturbances were apparently entirely secondary and disappeared when the psychological data were understood and educational pressures were reduced. As far as we know the problems which arose in school never interfered with a cheerful and well-adjusted home life. Certainly the mother never asked for help in this regard and we never forced help upon her.

Case 2. Pneumococcus meningitis; brain abscess. A. entered the Infants' Hospital for the first time at one year. As far as could be determined, the child was normal at birth, but did have convulsions on two occasions months before the onset of the febrile episode which caused her admission. Pneumococcus meningitis was found. By resourceful use of specific serum the infection in the meninges was controlled, but the child did not recover promptly. An encephalogram was done after four weeks with the hope of finding evidence of walled-off exudate. Aside from moderate dilatation of both ventricles nothing was found. After four more weeks the child developed a hemiplegia and signs of intracranial pressure. A frontal abscess was recognized and aspirated. Treatment was effective and the child promptly recovered without neurological or psychological evidence of defect. At this point the situation was remarkable but not confusing. During the course of the disease ventricular punctures had been necessary so that there was nothing mysterious about the abscess. Recovery was unusually satisfactory and appeared to be complete.

After all signs had disappeared we saw the child at intervals and she was next brought

into the hospital wards five months later with unilateral convulsions which promptly subsided. Except for out-patient supervision for colds we saw relatively little of the child for several years since the mother took her to various hospitals for advice.

At 23 months she was admitted here for uncomplicated otitis media. She walked and talked well at 2 years and the family had no complaints about general adequacy. At 3 years she was unconscious following a fall and was in another hospital for several days. She also was hospitalized elsewhere for a severe burn on the legs at seven years.

This stormy story of repeated physical episodes was supplemented by information from the Habit Clinic directed by Dr. Douglas Thom. His contact was the result of serious disturbance of behavior which began at 3 years of age. Running away was an outstanding and recurrent manifestation. She was taken to a State School for the Feebleminded, but her intelligence quotient in the eighties and the unwillingness of the family terminated this solution.

At $8\frac{5}{12}$ years she was readmitted to this hospital for study. Neurological examination was essentially negative.

The psychological situation can be briefly summarized. At 15 months, before discharge after the acute encephalopathy she showed interest in a variety of test materials. In general her responses were characteristic of 12 to 15 months behavior. At the Habit Clinic at $4\frac{7}{12}$ years she had an I.Q. of 81. A few months later a state school reported an I.Q. of essentially the same level. On admission here at $8\frac{5}{12}$ years the mother reported that she believed the child was intelligent but unmanageable. She "does everything on impulse . . . doesn't stick to anything . . . quarrels, insists on her own way. If they don't give her what she wants she gets hysterical, bites herself. I have to give in to her . . . twin brother thinks I like her better than him . . . he's got an inferiority complex." The mother did not trust her alone on the street because "she'll go with anybody that would speak to her." In the ordinary daily routine the child did not present major management problem; she was restless and impulsive. A demand out of the ordinary, such as a physical examination, demonstrated the child's emotional instability.

The child came willingly to the examining room and presented no problem, she answered promptly within limits of comprehension the tests. On Stanford-Binet rating her mental age was $6\frac{4}{12}$ years (C.A. $8\frac{5}{12}$), I.Q., 77. The outstanding defect was in the tests of immediate memory. This defect was further observed during the periods of teaching. The teacher at the hospital on three different occasions spent a long time trying to teach her a simple verse without success.

In spite of this memory defect, the child could read glibly, although inaccurately, in a second grade reader. She would add by counting on her fingers but as one would expect she had not been able to learn number combinations automatically. She could spell many words on a first grade level but if she had not learned the word her attempts to spell were phonetically poor; that is (did) = "d—e—a—l", (play) = "p—a—l—d". Her writing was quite variable; at times it was neat and well formed, at other times large and uncontrolled, occasionally there was a combination of writing and printing. She was not prepared for second grade work. The psychological situation was summarized as follows:

Mentally inadequate, rating variable, around 75–81. Emotionally unstable.

During a period of observation in the hospital at $8\frac{5}{12}$ years she was active and restless and was not easy to manage. Under the rather unexacting routine of the ward she could be controlled most of the time but had periods when she was inattentive and distractable and at times she was actively disobedient. She was strikingly unreliable and could not be depended on to carry out simple tasks. On the other hand she was agreeable enough and no one disliked her.

An encephalogram showed almost complete restitution of brain mass though there was demonstrable asymmetry of growth. The midline structures were slightly dislocated, presumably as a result of unequal growth of the two hemispheres. The presumption of course was clear enough that the behavior was the result of brain damage. It was assumed that the I.Q. of 80+ might represent a loss of intellectual assets.

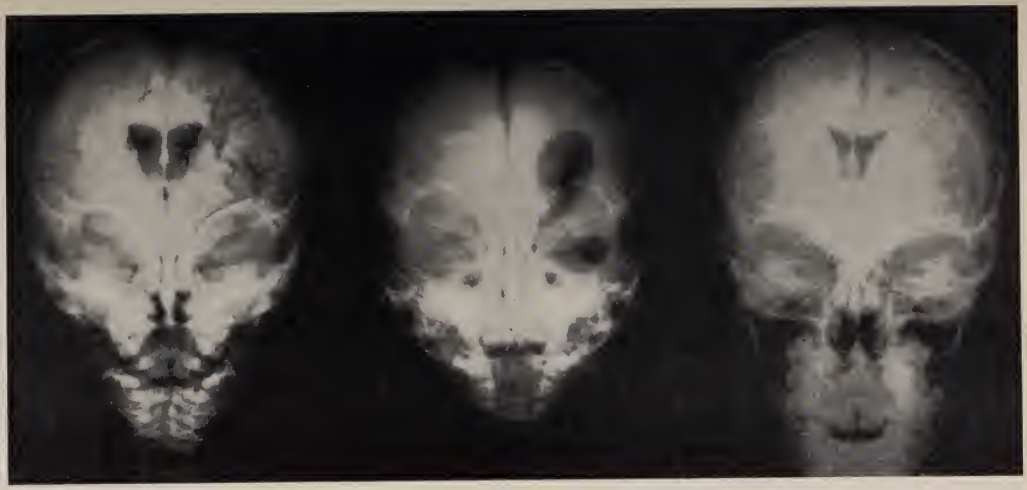

FIG. 1 FIG. 2 FIG. 3

FIG. 1. Case 2. Twenty days after onset of meningitis before evidence of brain abscess.
FIG. 2. Case 2. Thirty-seven days later after brain abscess had developed.
FIG. 3. Case 2. Films seven years later showing restitution of brain mass with slight asymmetry and apparent atrophy of the affected side.

Since the only solution acceptable to the family involved keeping the child at home, a serious study of the family was entered upon. This revealed a most complicated situation with the discovery that the mother had made contact with another social agency at 16 years. Her psychometric status was inadequate with an I.Q. of 80. A half sister of the patient had also been examined and was found to have an I.Q. of 88.

Conferences with other social agencies and repeated contact with the family revealed a series of events of a type only too familiar to this audience. In spite of deviations from generally respected standards the family seemed cheerful and tolerant. The very defects of the social setting helped the family to take the disturbing conduct of this child with amazing serenity. The other children did reasonably well and took the occasional convulsions of the child as much in their stride as they did the occasional appearance of the police, who patiently retrieved the child when she strayed too far.

Finally the patience of neighbors and the police was stretched to nearly the breaking point when she twice appropriated strange babies who were unattended and took them home with her. The fact that she gave them good care did not mollify the parents nor did it entirely satisfy the hitherto tolerant police force.

In going back over this record it is hard to reach definite conclusions. Taking the situation as it stood before the illness, we have a baby with at least two convulsions, in a family with various sociological and intellectual deficits. It is not unreasonable to assume that such an infant in such a family might have developed into the child we have described. On the other hand, the rest of the family have used almost equally limited intellectual assets more acceptably. Certainly any child, however promising, after such a savage insult to brain tissue might have deviations of conduct explained on the basis of encephalopathy.

It is interesting to speculate on the manner in which the frontal lesion may have altered the behavior pattern in this child. It is known that it is possible to resect or undercut parts of the frontal lobe without producing gross diminution of intelligence. The patients subjected to this procedure are expected to be easy to live with, but worry less than before and tend to be satisfied with modest standards. In this case the child is going along at the mediocre, intellectual rate which might have been predicted for her if no cerebral injury had occurred. Her deviations from her predicted course can be logically explained by a structural deficit which has reduced her judgment and sense of responsibility.

From the point of view of further supervision it is striking that the easy going acceptance which has been so characteristic of the family has been an asset up to now. It is entirely probable that tolerance at home will begin to be less useful from now on. Certainly the tolerance of the rest of the community has worn thin and is a bit brittle.

The reaction of the neighborhood, as observed by a reporter, is as follows:

"CHILDISH 'MOTHER LOVE' BRINGS KIDNAP SCARE

A two months old baby boy cast a faint smile at 10 year old A. from his carriage outside a market yesterday afternoon so A. wheeled him home prouder than Mrs. Dionne.

A minute later the baby's mother left the market and found her son gone. She screamed he had been kidnapped. Some one sounded a fire alarm and in another moment the section was packed with fire engines, cruising cars and more than 40 patrolmen and detectives.

Meanwhile A. was playing the little mother to the baby at her home. She changed his wet clothing, changed the orange juice in his bottle to water and was singing him to sleep when the anguished mother of the infant discovered them.

A.'s mother had gone to the motion pictures with her other children and was unaware of her daughter's escapades.

In her distracted state, the baby's mother went to the home of her mother-in-law, to report the loss of her son. Three hours later an unidentified boy went there and told her he knew where the girl who wheeled the baby away lived. The mother went there and found her boy chuckling in his usual good health. The police were called off.

A year ago A. let her motherly instinct get the better of her in another part of town. She took a child from there to her home and upset another mother for three hours."

These cases are, of course, unusual, but we are recurrently faced with a somewhat comparable situation. Children are admitted with signs of definite cerebral damage. Gross changes are sometimes seen on pneumoencephalography. Doctors are inclined to feel that they can define the deficit and judge prognosis on the basis of single observations supplemented by follow-up after a period of weeks or months. Two major difficulties are not always appreciated: First, it is, we believe, quite impossible to separate cases seen in the acute phases into one group where no further change is likely to follow and a second group where favorable or unfavorable changes are to be expected. Until recurrent observation, often over a period of years, has been carried out, it is frequently impossible to give an opinion which is valid about true recovery.

The second point is even more difficult to manage. After apparent recovery it may seem scientifically desirable to reappraise a child at intervals. Such reappraisal may keep the child, the parents and even the school from settling down with serenity to the job of education. It is possible to sympathize with an annoyed teacher who wrote the following letter.

She wrote: "During November, I received a letter from you inquiring about J. We find her to be a bright well-behaved child. Ever since entering school she has been in the highest class. She shows high mentality in all subjects. Her behavior in school and playground has been perfect. In fact, I'd say she is a normal healthy child. My belief is that the mother is carrying the story of J.'s lead poisoning too far. The child ought to be allowed to forget it as long as she is cured of it. Telling each teacher when the child seems all right is rather foolish unless she becomes ill again. So from our standpoint J 'carries on' as any regular smart child would." (Signed by the Acting Principal.)

It happens that recurrence of symptoms after the writing of the letter justified the curiosity of the psychological and of the medical minds but the letter makes a point nevertheless.

COMMENT

These cases are reported for two reasons. In the first place they are of some medical interest in themselves. The second and more important reason is that they illustrate the difficulty in following up patients in a general hospital. It seems possible that persistent following of all cases would confuse many children, parents and teachers. On the other hand persistent work is necessary if the criteria for estimating recovery are to be improved. In any case a question for debate can be set "What criteria for recovery after encephalopathy shall be accepted?" Our suggestion is that evidence of restoration to adequate growth in intelligence and emotional stability in addition to motor competence is the only valid one.

RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF RUPTURED INTERVERTEBRAL DISKS

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There can be few more remarkable examples of the excellent results that accrue from intelligent intensive cultivation of a surgical field than that of ruptured intervertebral disks. Twelve years ago a ruptured intervertebral disk was unknown (1). Now it is a clinical entity with precise definition, exceedingly common and curable by operative means without risk or loss of bony structure. Neurosurgeons now see more ruptured intervertebral disks than any other lesions.

This entity accounts for an overwhelming percentage of the hitherto incurable and untreatable low back pains and sciaticas, and miscalled sacroiliac strains, arthritis of the spine, etc., all of which must have been anathema to orthopedists. To have reached the present stage in diagnosis it is to be expected that many diagnostic tests should have been introduced and subsequently become unnecessary. And it is equally obvious that the operative treatment should become greatly simplified.

At first this lesion was localized by injecting small amounts of lipiodol into the spinal canal. For the detection of the smaller protruding disks by filling defects large amounts (5 cc.) of this substance were introduced by Mixter and Barr (2). Unless subsequently removed lipiodol is a permanent deposit in the subarachnoid space, both spinal and intracranial, and also has free access to the entire ventricular system. Reichert (3) (1937) introduced air as a contrast medium in order to avoid the huge masses of lipiodol. With good x-rays and excellent interpretation of the air shadows, the results were almost as satisfactory. The most important advance was attained through a statistical study of these lesions. Simultaneously and with identical results, and appearing in the same issue of the Archives of Surgery (1940), Love (4) and Spurling (5) found that 96 per cent of all spinal ruptured disks were at the fourth and fifth lumbar vertebrae. And if only lumbar disks were considered over 98 per cent were in these two situations. This at once simplified the localization of the lesion to one of almost absolute precision and entirely eliminated the need of spinal contrast media for its *localization*. However, this fact did not alter the need for a means of *diagnosing* the lesion. Semmes (6), emphasizing the characteristic clinical picture of ruptured disks, suggested that no spinal injections were necessary. He reported sixteen consecutive cases operated upon without contrast media or other tests, and at operation found the disks in all cases.

Three important advances have improved upon and greatly simplified the operative treatment. Originally (1) a bilateral laminectomy was performed and the disk removed intradurally. Mixter and Barr (2) removed the disks extradurally, but still used the bilateral approach. Semmes (6) and shortly afterwards Love (7) reported their removal by hemilaminectomy and by remov-

ing only a notch of bone in a lamina, and finally Love (4) removed a high percentage of ruptured disks through the interlaminal space without removing any bone whatever. Love's procedure is the acme of perfection, but can be accomplished only when the variable space between the laminae is of sufficient size. Practically it does not matter whether a small bite of a lamina is removed for better exposure.

CONCEALED VERTEBRAL DISKS

In a recent publication (8) the writer disclosed a variation of this lesion which was called a "concealed disk" and which represents about one-fourth of the total number. Symptomatically there was no difference whatever in the subjective or objective manifestations, but at operation the detection of the lesion was much more difficult. The end-results in treatment were precisely the same. A concealed disk is one that protrudes so slightly that it could hardly be found at operation unless one explored the subdural region with great care, but at the same time the findings are just as definite and unequivocal as the large protruding disks. Always there is a very tiny bulge of the intervertebral space with thickening of the spinal ligament; it indents with pressure of the forceps and gives a sense of fluctuation to the pressure of the forceps. And when incised the forceps dip deeply into a cavity in the disk. When a curette is introduced macerated vertebral disk is obtainable. In none, however, does a sizeable sequestrum of cartilage extrude through the opening. At times the concealed disk is laterally placed, at other times, at or near the midline. In every case the emerging nerve has been quite adherent to it, and this attachment is, I think, responsible for the pain; perhaps an intermittent protrusion of the disk may be a factor but there is no proof of this, and the seeming inelastic nature of the ligamentous capsule would appear to deny it.

There are always two component parts of a ruptured disk that are responsible for the patient's symptoms 1) the necrotic interior of the disk, under pressure from edema, causes the backache, and 2) the protrusion upon or adherence to the emerging spinal nerve causes the sciatica.

The realization of these two elements is necessary for the certainty of a cure. A large protruding disk may be withdrawn and still not cure the symptoms. It is all important that the interior of the disk be opened. It is not necessary to completely remove the contents of the ruptured disk to produce a cure—that is in fact impossible, but it is necessary to open it as widely as possible in order that the now viable content, i.e., the sequestrum, may be subsequently extruded through this opening. The principle in treatment is not unlike that of an abscess although the fundamental pathology is in no wise similar. There is no infective basis for an intervertebral disk. Always it is a traumatic aftereffect, and curiously, the trauma is always relatively slight. Curiously a severe traumatic rupture of the spine never causes a protruding disk. The explanation is, I think, that with severe injuries the ligament over the dorsal surface is torn and provides the vent for its cure much like the surgeon produces by incising this ligament and opening the interior.

A ruptured vertebral disk is one of the most satisfactory lesions to treat surgically. When properly treated a cure can be expected in almost every case, and spontaneous cures, or treatment by braces, etc., must be rare indeed. Recurrent attacks are to be expected throughout life, or at least for many years. From the postoperative follow-up reports in the literature there has been 5 per cent recurrence. So far I have not had a recurrence. This may be just a

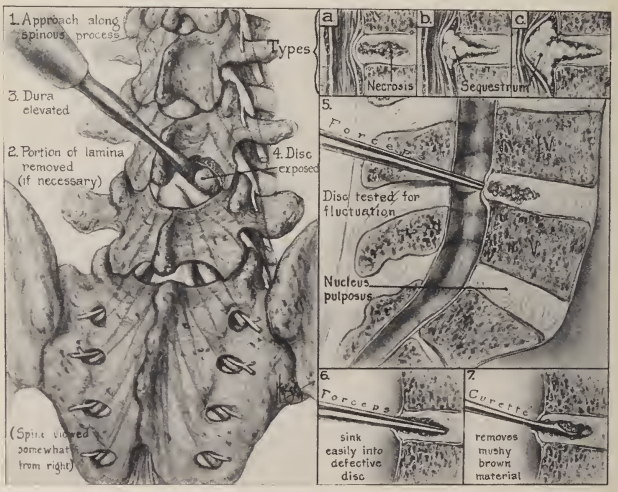

Fig. 1. Sketch showing the method of attack upon ruptured intervertebral disks (figure on left). Frequently the removal of this small portion of bone is not necessary (Love's procedure). The figures on the right show the three degrees of protrusion of the vertebral disk (a, b, c). Figure 5 shows the very slight elevation of a concealed disk and the indentation by pressure on the posterior spinal ligament. Figure 6 shows the defect in the disk itself. It is the wide opening of this that is necessary for the cure of the disk, whether of the protruding or concealed types. Curettement of the interior of the disk is not necessary, but in the concealed type one may obtain necrotic cartilaginous remains from the cavity. I see no reason to believe that the nucleus pulposus has any relationship to this lesion which involves much of the interior of the disk.

fortunate series, but I am inclined to believe that the explanation of recurrences is the failure to open the cavity in the body of the disk. Cures may result almost immediately, or they may take several weeks or even months; the difference, I think, is due to the time required for the complete extrusion of the affected disk. Bony fusion has been recommended by some operators, but this is neither necessary nor advisable. Patients should perhaps wear a brace for three months after operation and should avoid heavy lifting and back strains during this time; thereafter they may continue in any occupation.

The diagnosis of ruptured intervertebral disks is now one of the greatest simplicity and accuracy from the symptoms alone. The characteristic story is low back pain spreading down the posterior aspect of one, or at times both legs, intensification of the pain in the back and leg by coughing or sneezing. The only item of importance in the examination is the reduction or loss of Achilles reflex on the affected side. At times there may be hypesthesia along the course of the affected nerve. Given this story there can scarcely be any other lesion that need be considered. The pain begins after a heavy lift, a sudden twist of the spine, or an accident to the spine, or the trauma may even pass unnoticed. Movements of the spine intensify the pain. The pain is usually in recurring attacks with more or less free intervals between, but the pain may be continuous, and in many cases it eventually becomes constant. With continuous pain a psychoneurosis is a possibility; this and very occasional tumors (I have encountered one) are almost the only lesions that need be considered in differential diagnosis. At times the pain may be in the sacroiliac region on one or both sides; occasionally there may be no back pain, and intensification of the pain by coughing and sneezing may be absent, but when present it leaves no doubt of the organic nature of the pain when a psychoneurosis is under consideration. The presence of normal Achilles reflex means nothing; the reduction or absence means a great deal; its loss may be referable to either the fourth or fifth disk.

Another anatomical factor must be borne in mind, namely, the not infrequent occurrence of a sixth lumbar vertebra, and when present the ruptured disk will probably be at the sixth disk. Two of our cases in this recent series occurred in this position; it was only at the operation that the sixth vertebra was recognized and subsequently checked by x-ray.

I am particularly anxious to emphasize the purely clinical diagnosis and to deprecate the use of all contrast media in the spinal canal, even to avoid spinal punctures. In the first place these procedures are not necessary; they add nothing but the actual visualization of a lesion that is perfectly well known. They are painful procedures and no one would desire a permanent deposit of lipiodol in the central nervous system. It is true that much of the lipiodol may now be removed at the time of operation, or when operation is not performed, by another puncture and aspiration, but the latter may be only partially successful and is again very painful.

The most important reason, however, for avoiding spinal contrast media is that the results are frequently negative when an actual ruptured disk is present. It is here that the "concealed disks" are all important. None of them can possibly show a filling defect in either the air or lipiodol shadows; and concealed disks are more than 25 per cent of the total number. If lipiodol is used and is negative, it means that these patients are excluded from the operative treatment that is essential for a cure; and without lipiodol they are diagnosed with ease and certainty solely by analyzing the patient's symptoms.

It is the recognition of the concealed disks that has completed the solution of this problem which approaches 100 per cent in accuracy of diagnosis. Before they were known there was a corresponding percentage of negative explorations,

or, if lipiodol was used, a prosimilar percentage of patients who were denied operation.

Since the elimination of contrast media, we have had (since April 1, 1941 to the present time) by clinical examinations alone 65 cases without a single mistaken diagnosis. Lipiodol and air injections into the spinal canal, therefore, do far more harm than good, and their avoidance is most enthusiastically welcomed by the patient. In view of the fact that 96 per cent of all vertebral disks are at the fourth, fifth (and sixth) lumbar spaces (the percentage of the lumbar disks that are at these spaces is even greater), and since the unilateral approach is adequate to disclose the disk, regardless of the interspace involved, it only remains to make the diagnosis of a lumbar vertebral disk, and this is almost pathognomonic from signs and symptoms alone.

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DISTURBANCES IN LIPOID METABOLISM AND THE CENTRAL NERVOUS SYSTEM[1]

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The study of diseases of lipoid metabolism is concerned with three main groups (amaurotic family idiocy and Niemann-Pick's disease, Gaucher's disease and xanthomatosis), in accordance with the type of lipoid deposits. It received its impetus in 1887 when Dr. Sachs (1) described clinico-pathologically a case of amaurotic familial idiocy under the title of "Arrested Cerebral Development with Special Reference to its Cortical Pathology." The pathogenesis of this and allied disorders remained nosologically uncertain for a long time until it was ascertained that they were the result of disturbances in lipoid metabolism.

Because of the close relationship of these diseases, a brief review of the subject is timely. Illustrative cases belonging to these groups will be described briefly with special emphasis on the generalized disturbance of lipoid metabolism.

AMAUROTIC FAMILY IDIOCY AND NIEMANN-PICK'S DISEASE[2]—CASE REPORT

History. A. N., an 18 month old male infant, bottle fed from birth, gained rapidly and weighed 31 pounds at the age of 7 months. At that time, the mother noticed that the child was apparently blind, showed great irritability and would become startled by any sudden noise. He failed to keep his head erect or to attempt to sit or raise himself. At the age of 8 months, there appeared generalized convulsions with frothing at the mouth. The family history was negative for neuropsychiatric or hereditary disorders. The father, ten years before the death of this child, had had a splenectomy because of purpura hemorrhagica.

Neurologic examination. At the age of 18 months, the child, of fair complexion and slightly obese, was unable to speak or understand the spoken word, to stand or sit or hold his head erect. He did not respond to his environment nor would he grasp things placed in his hands. There was paralysis of the neck muscles, hyperactive deep tendon reflexes of the lower extremities with positive bilateral Babinski and Rossolimo signs. When placed on his abdomen and then returned to the position of lying on his back, he often showed "stretching" movements of all extremities and suckling movements, either with or without the use of his hand as a stimulus. Sudden noises caused startling movements. The fundi showed pallor of the discs, especially over the papillo-macular bundle and cherry-red spots in the macullae surrounded by a hazy gray area.

Laboratory data. All tests were negative except for a high lymphocytosis.

Course. Shortly after admission the patient ran an intermittent fever, sometimes as high as 104°F., the cause of which could not be ascertained.

Necropsy findings: Gross. There was generalized edema of all organs. The liver and spleen were not enlarged.

Microscopic. The liver revealed cloudy swelling of the parenchyma cells with considerable fatty infiltration. The lipoid deposits were more pronounced in the center of the liver lobules around the region of the central veins (fig. 1). The Kupffer cells also contained

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[2] As a result of the absence of a case of Niemann-Pick's disease, only one of amaurotic family idiocy with generalized lipoidosis will be described.

heavy deposits of fat; this was best demonstrated with the Smith-Dietrich stain. The lipoid deposits in the liver cells stained with Sudan III were paler than ordinarily seen in areas of degeneration. Some of these cells were vacuolated and had a xanthomatous appearance.

In sections of the spleen, in the Sudan III and Smith-Dietrich preparations, the Malpighian corpuscles were surrounded with heavy lipoid deposits (fig. 2). Groups of foam, reticular and degenerated cells were found in some of the small Malpighian corpuscles

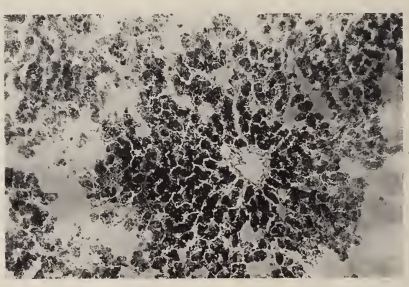

FIG. 1. Lipoid deposits of liver cells around a central vein (Sudan III, × 100)

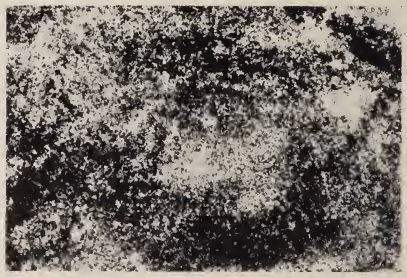

FIG. 2. Malpighian corpuscle of the spleen surrounded by lipoid deposits (Smith-Dietrich stain, × 70).

(figs. 3A, B). The foam cells contained fatty deposits consisting of pale red staining material similar to that found in the nerve cells of the cortex. The cells in some of the folliculi also contained deep red staining material which were identified as products of disintegration. Some of the cells in the center of the Malpighian corpuscles were swollen, vacuolated and had a xanthomatous appearance (fig. 3B).

Central nervous system: Gross. The brain weighed 1280 grams. The greatest enlargement was in the parietal and occipital regions. The convolutional pattern was normal. The cerebellum was slightly larger than normal. The corpus callosum was thin.

Microscopic. Throughout the central nervous system, there was a poverty in the myelin with occasional disintegration of some of the myelin sheaths. This was noted in the white matter of the cerebral hemispheres, the internal capsule, striopallidal fibers, pallidonigral

fibers, optic tracts and mammillo-thalamic bundle. The pallidal segments were paler than normally. In sections through the mesencephalon and pons, there was pallor of the pontine fibers and the pyramidal tracts. The cerebellar pathways such as the brachium conjunctivum, corpus restiforme and the sensory tracts stained normally. In the spinal cord, the posterior columns and cerebellar tracts stained well while the pyramidal, rubrospinal and Helweg's tracts stained poorly.

In the cresyl violet preparation, the nerve cells of practically all the structures were extensively swollen. With lower power, the swollen nerve cells gave the sections a honeycombed appearance best seen in myelin sheath and Bielschowsky preparations. Some of the nerve cells were pear-shaped; others were ovoid or fusiform and contained practically

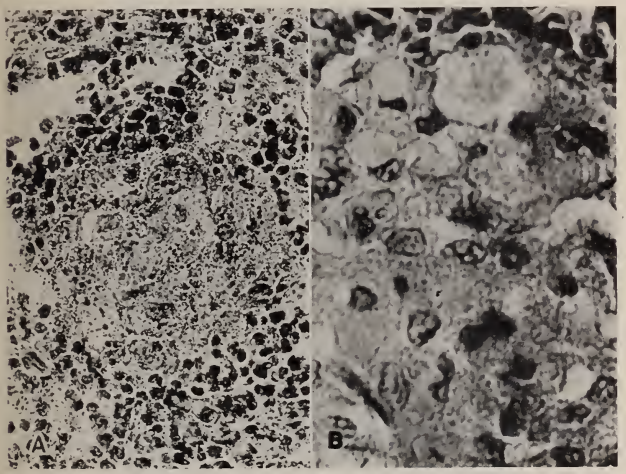

FIG. 3A. Foamy reticular and degenerated cell within the Malpighian corpuscles of the spleen (Sudan III, × 400).

FIG. 3B. Same as 3A. Notice their xanthomatous appearance (Hematoxylin-eosin stain, × 800).

no cytoplasm (fig. 4). These had a granular and reticular appearance. The nucleus was generally displaced at the periphery and the nucleolus stood out prominently (fig. 4). Many of the nerve cells consisted of one large peripherally displaced nucleus and a prominent cytoplasmic membrane (fig. 4). The glia cells were also partially swollen and their nuclear membranes stained poorly. The Purkinje cells were also swollen and showed absence of pericellular fibers and swelling of the dendrites and axis cylinders (fig. 5). The neurofibrillar structure in most nerve cells was completely gone but in some they collected at the periphery. The body of many nerve cells was filled with fine silver granules. The axis cylinders between the various cellular structures appeared preserved. A slight gliosis was observed in the areas of demyelination. In the Sudan III preparation, the nerve cells were filled with pale rose colored material. The same was true of the glia cells but the fatty deposits in some of these consisted of deeply stained red material which undoubtedly were products of disintegration.

Comment. A satisfactory knowledge of the pathogenesis of amaurotic family idiocy and Niemann-Pick's disease was first arrived at when Niemann (2) in 1914 and Pick (3) in 1926 described the histopathologic changes in this new disorder, in which in addition to the enormous hepatosplenomegaly and cachexia, there was a generalized deposition of lipoids in the entire reticulo-endothelial system. The close relationship of amaurotic family idiocy to this disorder was

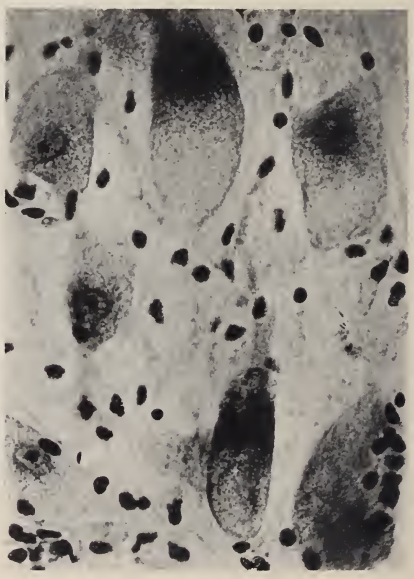

FIG. 4. Swollen nerve cells. Notice the poorly stained Nissl substance, the granular and reticular appearance. The nuclei are displaced at the periphery and the nucleolus stains deeply (Cresyl violet stain, × 400).

first demonstrated by Knox, Wahl and Schmeisser (4) and Hamburger (5). Pick and Bielschowsky (6), in 1927, restudied Hamburger's case. Bielschowsky (6) was able to demonstrate that the central nervous system lesion was the same as in amaurotic family idiocy, and that the contents of the nerve cells as well as those demonstrated in the spleen had the same affinity for hematoxylin. Finally a number of investigators, Bielschowsky (7), Sachs (8), Marinesco (9), Spielmeyer (10), Kufs (11) and others came to the conclusion that the generalized lipoid histiocytosis in all the organs, especially the liver, spleen and lymph nodes,

and in the central nervous system seen in Niemann-Pick's disease is the result of a disturbed lipoid metabolism which causes an abnormal accumulation and distribution of lipoid in the cells. The swelling and the other histologic changes were considered to be secondary to the accumulation of lipoid in the cell. Schaffer (12), who has contributed extensively to the knowledge of this subject, still insists that amaurotic family idiocy and generalized lipoid histiocytosis are not produced by the same causative factor. Furthermore, he believes the swelling

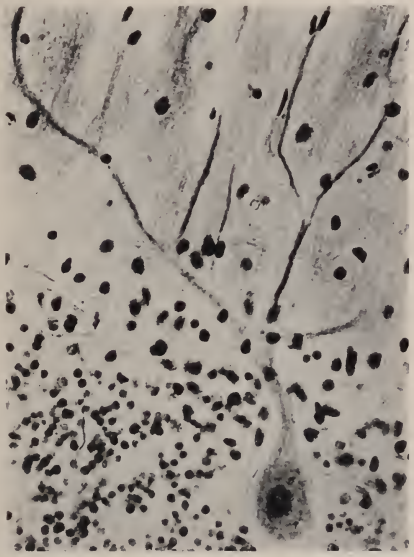

Fig. 5. Swollen Purkinje cell. Notice the absence of neurofibrillae, the deeply stained and prominent nucleolus and the swelling of the axon and dendrites (Bielschowsky stain, × 480).

of the nerve cell to be the result of decomposition of the hyaloplasm (the undifferentiated part of the cellular cytoplasm) into its basic elements of proteins and lipoids.

Kufs (11), Böhmig and Schob (13) and Davison and Jacobson (14) were able to demonstrate, in cases of amaurotic family idiocy, lipoid deposits not only in the central nervous system but also in other organs, such as the spleen, liver and other lymphoid organs. Although the spleen and liver were not enlarged except in Böhmig and Schob's case, the character of the lipoid deposits in the reticuloendothelial system was the same as that found in the nerve cells.

The intracellular chemical constituents of these lipoid deposits in the nerve and reticulo-endothelial cells were further investigated and found by Bloom (15) and Brahn and Pick (16) to be phosphatides, mixed with neutral fat and a slight amount of cholesterol. Epstein (17) suggests that the phosphatid deposits are the result of a disturbance of the neuro-endocrine regulation of the lipoid metabolism. He is of the opinion that there are two types of Niemann-Pick disorders, one with changes in the central nervous system associated with amaurotic family idiocy and one without amaurotic family idiocy. He also believes that there is a pure form of amaurotic family idiocy without lipoid deposits in the spleen, liver and other organs. In 1934 Epstein (17) reinvestigated three other cases (Santhos (18) and Marburg (19)) and he came to the conclusion, from the chemical point of view, that the cerebral changes in Niemann-Pick and pure amaurotic family idiocy were not the same for he was unable to find in the latter an increase in the cerebral lecithin. In Bauman's case of Niemann-Pick with a cherry red spot Klenk (20) was able to demonstrate that the principal stored lipoid was not lecithin but sphingomyelin, thus establishing a closer chemical relationship between Gaucher's and Niemann-Pick's disease. In Gaucher's disease there is a galactose combination, whereas in Niemann-Pick's disease there is a combination with choline-phosphoric acid which belongs to the lignoceryl-sphingosine group. Tropp and Eckhardt (21) recently were able to isolate sphingomyelin in the same proportions as Klenk; they considered Niemann-Pick's and amaurotic family idiocy as closely allied disorders, without being able to state definitely whether they are one and the same disease.

GAUCHER'S DISEASE[3]—CASE REPORT

History. F. S., a man, aged 26, Jewish, born in Poland, suffered from generalized arthritic pains since 1921. In 1922 an enlarged spleen was noted. A splenic puncture and histopathologic examination lead to a diagnosis of Gaucher's disease. Later, there occurred nasal and oral hemorrhages, enlargement of the abdomen, anemia and occasionally urinary incontinence. Following a splenectomy in 1928 there was some improvement in the symptoms and the anemia. In 1928, however, there was a recurrence of the arthritic pain and in 1930 a gibbus in the dorsal region was noted. Enlargement of the liver was first noted in 1931. As a result of the vertebral involvement, the patient's height decreased from 60 to 54 inches. Since 1934 the patient was bed-ridden, weak and complained of severe pains throughout his joints and bones. At about the same time, there developed a pathologic fracture of the sternum and marked polyuria, which persisted until death in April 1935.

Examination. The patient was a malformed and poorly nourished individual with yellow-brownish discoloration of the skin. There was slight clubbing of the fingers and pinguecula formations in the inner canthus of both eyes. Small discolored painless nodules were found in the cervical, axillary and inguinal regions. There was a dorsal kyphosis extending from the sixth to the tenth dorsal vertebrae and lordosis in the lumbar region. The vertebrae in the kyphotic region were tender. There was dullness, increased tactile fremitus and moist râles at the base of the right lung. The liver was markedly enlarged; it was firm, smooth and tender and extended to the right iliac fossa. The bones throughout were painful to touch.

[3] Blood picture and general physical examination of this case were described in detail by Drs. S. Melamed and W. Chester: Osseous Form of Gaucher's Disease. Arch. Int. Med., 61: 798–807, 1938.

Laboratory data. Blood picture on various occasions disclosed marked anisocytosis, poikilocytosis, basophilia, polyehromasia, occasional Howell-Jolly bodies, and large abnormal platelets. At times, there was a tendency to macrocytosis with a few macroblasts. The blood studies disclosed severe anemia, with nucleated red blood cells, lymphocytes, myelocytes and myeloblasts. Calcium 10.4 mg. per cent, phosphorus 2.9 mg. per cent; blood cholesterol ranged between 130 to 180 mg. and the cholesterol ester 57 to 101 mg. per cent. Basal metabolic rates were plus 40, and plus 44. The liver function tests, blood bromsulfalein, disclosed 50 per cent of dye remaining in the blood after 1 hour indicating hepatic dysfunction. Urine analysis showed specific gravity 1.028, positive albumin, and marked increase in urobilin and urobilinogen. Bilirubin of blood was 0.3 mg. per 100 cc. The icteric index was 4. Roentgen examination of spine disclosed collapse of the fourth, fifth, sixth, and seventh dorsal and first and fourth lumbar vertebrae (fig. 6). The fifth vertebra

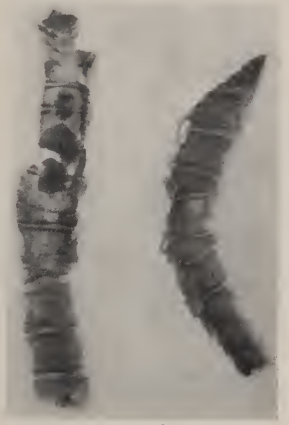

FIG. 6. Roentgenogram of spine disclosing collapse, destruction and absorption of various vertebrae.

was markedly destroyed (fig. 6). The body of the ninth vertebra showed marked absorption (fig. 6). The bodies of the seventh and eleventh dorsal and first lumbar vertebrae were collapsed to about one-third of their normal size with obliteration of the intervertebral spaces between the twelfth dorsal and the first lumbar. Cystic areas and areas of bone absorption, decalcification and sclerosis were noted throughout most of the bones of the body such as the pelvic, femurs, tibia, fibula, humerus, radius, etc. A pathological fracture of the first dorsal vertebra occurred January 15, 1935. The skull was normal.

Course. On December 1, 1934 a neurological examination disclosed slight increase in the knee and ankle jerks, more on the left side without evidence of Babinski or allied reflexes. There was a slight hyperesthesia over the right lower extremity and hyperesthesia on the left side between the eighth and tenth dorsal segment with hypesthesia below this level. The patient had an expressionless face without any tremor of the extremities.

Necropsy findings. General examination disclosed Gaucher's disease with involvement of the liver, lymph nodes, vertebral column, bones of the upper and lower extremities,

heterotopic bone formation and bronchopneumonia. The body of the sphenoid bone fragmented easily at autopsy. The hypophysis was normal in size but the posterior lobe was dark in color and gelatinous in appearance. The anterior vertebral column showed extensive infiltration and destruction of bone structures. Microscopic sections of the vertebrae especially the sixth and seventh dorsal disclosed numerous Gaucher cells in the medullary cavity.

Sella turcica. Sections through the region of the sella turcica were stained by the hematoxylin-eosin method. The adjacent bone was thinned out and invaded by reticular cells with irregularly shaped nuclei and a pale staining cytoplasm (fig. 7). Most of these had the typical xanthomatous appearance of foam cells seen in Gaucher's disease.

Central nervous system. The brain weighed 1460 grams. It had a markedly anemic appearance. The globus pallidus had a slight brownish discoloration. The spinal cord except for marked pallor showed no abnormalities.

Microscopic. Sections through the various convolutions, basal ganglia, mesencephalon, pons and spinal cord were stained by the myelin sheath and cresyl violet methods. Some sections were also stained with the Smith-Dietrich, Sudan III, Bielschowsky, and Holzer methods.

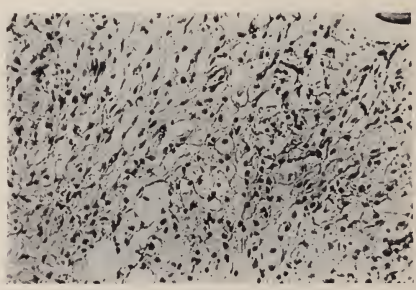

FIG. 7. Foam cells invading the sella turcica (Hematoxylin-eosin stain, × 200)

Sections through various convolutions showed a normal cytoarchitectural arrangement with occasional vacuolization of nerve cells and a few large pale glia cells. These glia cells were not surrounded by pigment granules. In sections passing through the striatum and pallidum, there were numerous pale glia cells, some of which were surrounded by fine and coarse pigment granules (fig. 8 A, B). These resembled Alzheimer glia cells type I and were found throughout the caudate, putamen and pallidum but were mostly numerous in the first and second segments of the globus pallidus. Many of the large nerve cells of the putamen and caudate nuclei disclosed loss of Nissl substance, swelling of their bodies and displacement of the nucleus to the periphery. Some of the nerve cells were completely disintegrated; there was only a slight preservation of the nucleus. The nerve cells of the thalamic and hypothalamic nuclei and other nuclear components of the diencephalon appeared normal. The dentate nuclei disclosed an occasional pale glia cell without any pigment granules; its nerve cells appeared slightly shrunken and pyknotic. The Purkinje cells although slightly swollen were normal. The pons and medulla oblongata appeared normal.

Spinal cord. There was a slight pallor of the fiber tracts in the region of the dorsal and ventro-spino-cerebellar pathways in the thoracic region. With high power, the myelin sheaths of these tracts were swollen and slightly disintegrated. In the cresyl violet preparation, large foam cells containing irregularly shaped nuclei usually placed at the periphery

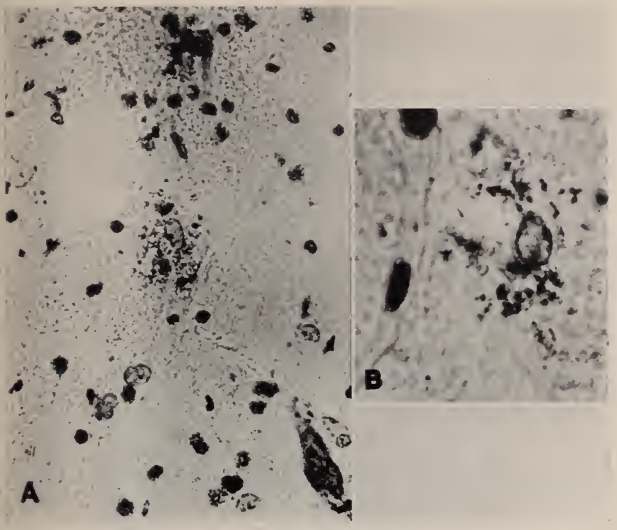

FIG. 8A. Alzheimer glia cells surrounded by pigment granules. Notice also the large pale glia cells without pigment granules (Cresyl violet stain, × 400).
FIG. 8B. Alzheimer glia cells surrounded by pigment granules (Cresyl violet stain, × 800).

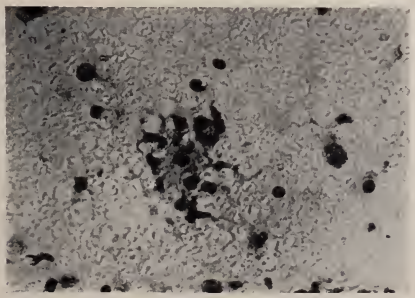

FIG. 9. Group of foam cells from the spinal cord (Cresyl violet stain, × 100)

and containing pale staining cytoplasm were seen in the spinal cord (fig. 9). These resembled the cells seen in the region of the sella turcica. Similar cells were also found in the posterior and anterior roots (fig. 10).

Comment. This case of Gaucher's disease is of interest because of the generalized involvement of various organs including the sella turcica, vertebral column, spinal cord and roots. The implication of the sella turcica with compression of the pituitary and the floor of the third ventricle accounted for the polyuria. The scanty neurologic findings referable to the spinal cord and roots were undoubtedly caused by the compression of these structures by the diseased vertebrae or by the infiltrating lipoid nodules. The expressionless face was the result of disease of the pallidum and striatum. The Alzheimer glia cells and nerve cell changes in the pallidum and striatum were analogous to those seen in hepatolenticular degeneration secondary to disease of the liver and spleen. Such changes as is well known are found not only in Wilson's disease or pseudosclerosis but also in many other diseases of the liver. The pathologic findings in the pallidum and striatum were secondary to disease of the liver and spleen and bear no direct relationship to Gaucher's disease.

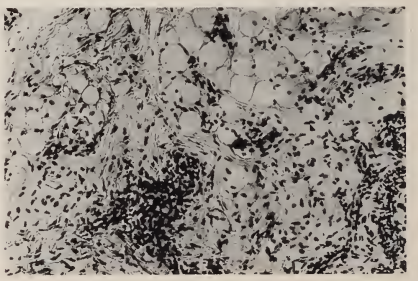

FIG. 10. Foam cells and inflammatory reaction in the region of the roots (Cresyl violet stain, × 100).

The chemistry of the lipoid in Gaucher's disease was reinvestigated when the relationship between amaurotic family idiocy and Niemann-Pick's was established. Eppinger (22) was the first to call attention to the close relationship between splenomegaly in Gaucher's disease and the role of the reticulo-endothelial system in lipoid metabolism. Mandelbaum and Downey (23), Wahl and Richardson (24), and Siegmund (25) were the first to demonstrate the increase of cholesterol and phosphatides in such spleens. Epstein and Lorenz (26) in 1924 showed that the predominating lipoid in Gaucher's disease consisted of a cerebroside while Lieb (27) in the same year succeeded in isolating the cerebroside kerasin. The presence of kerasin, however, could not be demonstrated in the central nervous system as it was in the spleen. All that could be shown was that this substance differed from the phosphatides.

Gaucher's disease which was originally considered as an affection of the spleen, skeletal and hematopoietic systems was also found to involve in a few instances the nervous system. Rusca (28) was the first to describe clinical neurological

findings in infantile cases of Gaucher's disease. His observations were confirmed by Reber (29), Dienst and Hamperl (30), Stransky (31), and Meyer (32). Abali and Kato (33) from a collection of 26 cases reported in the literature, in which the onset of the disease had taken place during the first year of life, found neurologic manifestations such as neck rigidity, opisthotonus, strabismus, laryngeal spasms, dysphagia, sensory loss, hypertonicity and catatonia in 18 cases. The first histopathologic changes in the central nervous system were demonstrated by Oberling and Woringer (34). Lindau (35) in 1930 described swelling of the nerve cells with slightly colored granular deposits, displacement of the nucleus to the periphery, dislocation of the neurofibrils and swelling of the dendrites. He insisted that these changes in Gaucher's disease differed from those seen in amaurotic family idiocy because of the non-sudanophile content and the absence of swelling of Purkinje cells. He believed, however, that Niemann-Pick and Gaucher's disease were pathogenetically the same, the result of disturbance in metabolism, possibly secondary to an endocrine disturbance and a congenital dystrophy of the mesenchyme.

The neural changes in Gaucher's disease except for the above reports by Oberling and Woringer (34) and Lindau (35) in breast-fed babies were never observed in children or adults. The case illustrated in this presentation is the first presenting neural changes in an adult suffering from this disorder. Swelling of the nerve cells and neurofibrillar changes as described by Oberling and Woringer (34) and Lindau (35) were not observed in my case. The nerve cell changes in the striatum and pallidum were not analagous to those described by the above authors and were unquestionably secondary to the cirrhosis of the liver.

XANTHOMATOSIS (SCHÜLLER-CHRISTIAN SYNDROME)[4]—CASE REPORT

History. P. S., a man aged 27, whose parents were Russian Jews, had a discharge from the left ear, a fistula in ano, and a sinus of the right thigh. He complained of polyuria and polydipsia, voiding as much as 11 liters of urine a day. The symptoms first started with looseness and falling-out of teeth and development of multilocular cysts of the lower jaw which on examination proved to be due to a granuloma of the reticulo-endothelial system. No other member of the family suffered from this disorder.

Examination. There was female distribution of pubic hair; absence of teeth except for two in the upper jaw; draining of sinus in the left axilla and left thigh; fistula in ano and enlarged liver.

Neurological examination. There were horizontal nystagmoid twitches in both directions; unsteady gait; diminished power in all extremities, more so on the right; generalized hyperreflexia; bilateral ataxia; suggestive Gordon-Holmes on the right; dysdiadokokinesis bilaterally; coarse tremor of outstretched hands and slight intention tremor of hands; questionable pallor of the right optic nerve head; hypalgesia, thermohypesthesia and hypesthesia over the left fifth nerve; impaired taste over the left anterior two-thirds of the tongue; peripheral paralysis of the left side of the face; slight diminution in hearing on the left and polyuria and polydipsia.

Laboratory data. Roentgen examination disclosed destruction of the inner and outer tables of the parietal bones (fig. 11), of the clinoid processes of the sella turcica, of the shaft of the right femur and of the right wing of the sacrum. Blood pressure, 100 systolic and

[4] This case was previously reported in great detail in the Arch. Neurol. & Psychiat., 30: 75, 1933.

66 diastolic. Blood serum contained: cholesterin 152 mg. per 100 cc. (normal from 150 to 190); total fat 1.71 per cent (normal 0.7 per cent); albumin 4.71 per cent; globulin 3.23 per cent; calcium 9.8 mg.; phosphorus 3.9 mg.; sugar tolerance test on fasting 89 mg.; 1 hour after meal, 110 mg.; 2 hours after meal 86 mg. The basal metabolic rates were plus 1 per cent and minus 4 per cent respectively.

FIG. 11. Roentgenogram of the skull showing destruction of the inner and outer tables of the parietal bones.

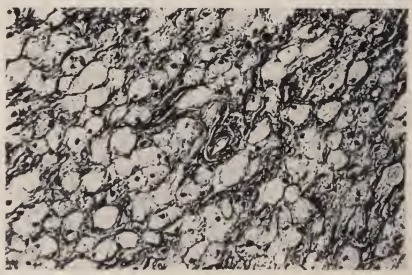

FIG. 12. Foam cells in the loose connective tissue outside the pituitary gland (Hematoxylin-eosin stain, × 100).

Necropsy findings: Gross. The calvaria of the skull showed a punched-out area of rarefaction in the parietal region (fig. 11). A large portion of the cortex of the bone in this region was eroded. Several irregular thickenings of the calvarium were found in the area of erosion. Grayish-yellow, stellate-shaped nodules were found in the lungs.

Microscopic. There were typical "foam cells" in the bone of the skull, right femur, mandible, maxilla; also in lungs and the pituitary gland.

Pituitary gland. In the loose areolar connective tissue outside the pituitary gland there was a collection of "foam cells" (fig. 12), with an occasional lymphocyte. The anterior

portion showed a striking decrease of oxyphilic cells. The region of the parts intermedia of the posterior portion was invaded by groups and islets of acidophilic and basophilic cells.

Central nervous system. Except for a slightly spongy appearance of the white matter of the parietal region, no gross abnormalities were noted.

Microscopic. The white matter of most of the cerebral convolutions and especially that of the superior parietal region showed scattered and confluent plaques of demyelination (fig. 13). The myelin in these plaques had completely disappeared and was replaced by irregularly shaped swollen cells. The demyelinated areas consisted of groups of large cells irregularly shaped with pale cytoplasm and irregular and darkly stained nuclei, generally situated at the periphery of the cell. Some of these cells contained vacuoles. Groups of typical foam cells were also noted (figs. 14A, B). Between some of the large foam cells there were numerous oligodendroglia and astrocytes. Numerous compound granular

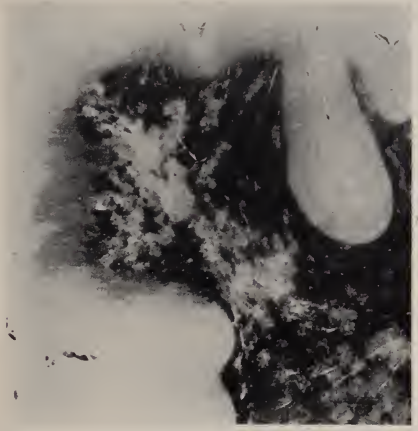

FIG. 13. Scattered and confluent plaques of demyelination in the white matter (Myelin sheath stain, × 100).

corpuscles were also present. The architectural arrangement of the cortical layers was well preserved. The nerve cells of the cortex showed no changes except for the sixth layer where some were destroyed and others stained poorly. With the Fett Ponceau, Smith-Dietrich and Sudan III stains, many of the foam cells in the white matter contained fatty deposits which stained lighter than the usual fatty deposits seen in compound granular corpuscles or areas of softening; some of the cells did not contain fat. Some of the substances stained for fat were doubly refractile. In the Bielschowsky preparation, the axis cylinders did not show the marked destruction seen in myelin sheaths. A few healthy axis cylinders were found. Some of the axis cylinders, however, were fragmented and had a corkscrew appearance. Others were slightly swollen. The destroyed areas were replaced by glia tissue. Other demyelinated plaques with similar changes were found in the white matter of the superior and inferior parietal, inferior temporal, hippocampal, dentate and fusiform gyri, splenium of the corpus callosum and optic radiation. In sections through the basal ganglia and hippocampus, plaques were found throughout the corpus callosum, internal capsule, anterior commissure, thalamus, globus pallidus, fornix, columnae fornices

and substantia nigra. Some of the nerve cells of the various nuclear masses were replaced by glia cells; others stained poorly and showed signs of disintegration. The tuber cinereum was replaced by areas of fibrosis and gliosis. Lymphocytic infiltrations were found at the

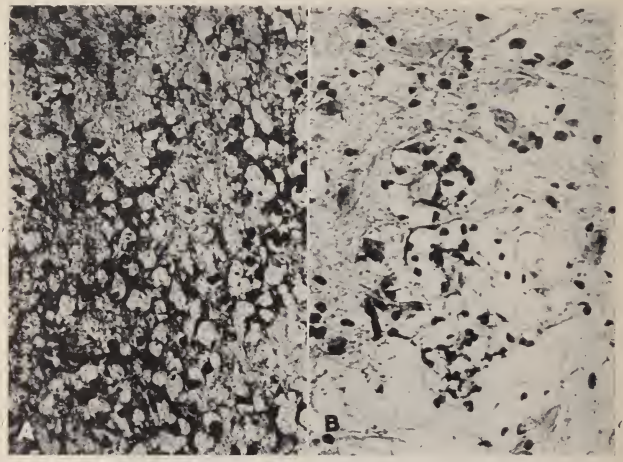

Fig. 14A. Foam cells in the demyelinated areas (Cresyl violet stain, × 100).
Fig. 14B. Group of foam cells in the demyelinated areas (Cresyl violet stain, × 200).

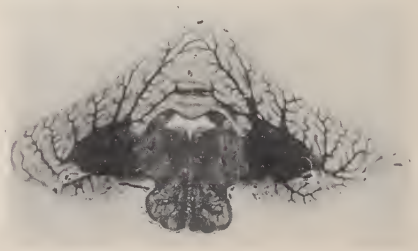

Fig. 15. Coronal section through the cerebellum and medulla oblongata disclosing scattered demyelinated plaques in the branchium conjunctivum and pontis, medial and lateral lemnisci, right pyramid and cerebellum (Myelin sheath stain).

periphery. A few vessels of the tuber cinereum showed perivascular infiltrations. The nerve cells of the various hypothalamic nuclei were reduced in number; the cytoplasm in some was pale without any Nissl substance and the nuclei were situated at the periphery. Swollen nerve cells which did not contain the normal amount of pigment were also present.

In the midbrain, pons, cerebellum and medulla oblongata, small scattered demyelinated

plaques were found in the lateral lemniscus, brachium conjunctivum, medial lemniscus, brachium pontis and pontine fibers (fig. 15), the left sensory nucleus of the fifth nerve, the nucleus of the seventh nerve and in the right and left fifth nerves as they emerged from the pons. The nerve cells of the left fifth sensory nucleus were diminished in number, some were poor in chromatin material while others were completely destroyed. The demyelinated areas showed the same histopathologic picture as described above.

Comment. Xanthomatosis (Schüller-Christian syndrome), a disturbance in cholesteral metabolism, consists of granulomatous, yellowish, "rubbery" masses deposited throughout most of the organs. For a long period the disorder was considered neoplastic, inflammatory or traumatic. Roland (36) in 1928 was the first to recognize that it was related to the reticulo-endothelial system and demonstrated its relationship to Gaucher's and Niemann-Pick's disease. Epstein demonstrated that the cells in these granulomatous masses contained deposits of neutral fat, cholesterin esters and free cholesterine.

The doubly refractile bodies in the fat filled cells, the high cholesterol content in the dural plaques, and the frequent high percentage of cholesterol and total fat in the blood support the theory that this disease consists of a disturbance in cholesterol metabolism.

The deposition in the dura, hypophysis, infundibulum, tuber cinereum and orbital fat are undoubtedly responsible for the diabetes insipidus, exophthalmus and other neurologic symptoms. Direct infiltrations in the central nervous system were described by Chiari (37), Davison (38), Van Bogaert, Scherer and Epstein (39) and Heine (40). Extraneural masses compressing the nervous system were also described by Thompson, Kegan and Dunn (41), Kyrklund (42) and Weidmann and Freeman (43). Chiari (37) reported granulomatous xanthoma nodules infiltrating the central nervous system mostly in the cerebellum; the white matter being more involved than the gray. In Van Bogaert's, Scherer's and Epstein's (39) cases, the lipoid deposits consisted of xanthoma cells and intra-and extra-cellular cholesterin crystals. The lipoid deposits of the nervous system had a focal and systemic distribution as in my case. In the focal lesions, there were giant cells and crystals. In the systemic, only xanthoma cells were present. They described involvement of the white matter of the cerebellum, occipital lobes, cerebral peduncles, pallidum, pyramidal tracts, olivocerebellar system, middle and superior cerebellar peduncles and optic nerves. Some of the lesions in the central nervous system such as the diffuse disappearance of the Purkinje cells and of some anterior horn cells are not to be considered as secondary to the lipoid deposits. In Heine's (40) case, the illness lasted 18 years; the patient died at the age of 50. In this case the lesions consisted of numerous small foci of demyelinization with dense gliosis, sudanophile and siderophile substances, compound granular corpuscles and inflammatory cells. He found these lesions in the gray and white matter, mostly in the white matter of the cerebellum and pyramidal tracts. The ganglion cells in these foci were frequently preserved. Heine considered this as a sclerosing encephalitis comparable to multiple sclerosis with secondary degeneration in the spinal pathways. He believed the foci to be residual states, healing stages of xanthomatous granulomas.

No doubt a number of the cases of xanthomatosis show neurologic findings and, if every case were studied carefully, changes in the nervous system could be demonstrated.

CONCLUSIONS

Amaurotic family idiocy, Niemann-Pick's, Gaucher's and xanthomatosis are affections caused by a disturbance in lipoid metabolism.

Amaurotic family idiocy and Niemann-Pick's disease are closely related. The deposition of lipoids in these disorders involves not only the central nervous system but also the entire reticulo-endothelial system. This relationship was not definitely established in all cases of amaurotic family idiocy. The more carefully one studies this disorder, the more apt one is to find a generalized instead of a localized lipoid disturbance as seen in the central nervous system. The lipoid deposits in the nervous and reticulo-endothelial systems consist of phosphatides. In Niemann-Pick's disease, a specific increase of sphingomyeline has been demonstrated.

Gaucher's, a disease of the reticulo-endothelial system, the result of disturbance in lipoid metabolism may occasionally affect the central nervous system. The predominating lipoid consists of kerasin belonging to the cerebroside group.

Xanthomatosis consisting of granulomatous masses deposited throughout most of the organs may also invade the calvarium, compress the nervous system or actually infiltrate it as reported in several instances. It's a disturbance in lipoid metabolism involving the reticulo-endothelial system; the predominating substance is cholesterol.

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OBSERVATIONS ON THE EFFECT OF TOCOPHEROL ON CREATINURIA[1]

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Muscular symptoms were observed by the first investigators of vitamin E deficiency in animals (Evans and Burr (3), Goettsch and Pappenheimer (8)). Goettsch and Brown (7), and Telford, Emerson and Evans (17), noticed a decrease of the muscle creatine content in these animals. These muscular symptoms are accompanied by creatinuria (Morgulis and Spencer (13)). Verzár (19) showed that creatinuria decreased in tocopherol deficient rats following the administration of large amounts of this vitamin.

Mackenzie and McCollum (11) observed that vitamin E deficiency induced urinary creatinuria in rabbits two weeks before clinical symptoms became manifest. Oral tocopherol administration for one or two days sufficed to diminish this condition markedly (cf. Eppstein and Morgulis (2)).

Studies conducted in this laboratory on the neurological symptoms and anatomical changes in monkeys while vitamin E was withheld from their diet will be reported elsewhere (Wechsler and Globus (21)). The animals received 460 calories daily, an amount considered adequate for monkeys (Tilden and Miller (18)). The diet was in the form of cookies, baked from a mixture of: 29.4 per cent of commercial casein, 36.7 per cent of autoclaved tapioca (dextrin), 22.0 per cent of commercial bulk lard, 11.0 per cent of dried Brewer's yeast, and 0.9 per cent of Hawk and Oser (9) salt mixture. This mixed diet is a slight modification of the vitamin E deficient diet prescribed by Evans, Murphy, Archibald and Cornish (4) and by Palmer (14). The lard was treated with a saturated ether solution of iron chloride in order to destroy traces of vitamin E. In addition the monkeys received about 5 ml. of orange juice, which was later replaced by 25 mg. of ascorbic acid daily. The cookies were supplied twice a day, morning and evening, and at noon the animals were given three lumps of sugar dipped in cod liver oil. The above diet seemed to be sufficient as the monkeys kept their weight and thrived well. During these experiments the urinary creatine and creatinine excretion was investigated in nine monkeys (8 Macaca mulatta, and 1 Macaca irus). Because of the simultaneous attempt to produce creatinuria and lesions of the nervous system, the periods of tocopherol deficient diet could not be interrupted for control studies. In three monkeys the excretion studies were started after the institution of the

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vitamin E deficient diet, and in two others, additional observations were made during a control period on a normal diet preceding the deficiency regimen. Besides, control data were obtained on four normal monkeys.

Table 1 summarizes the results of twenty observational periods consisting of three to twenty consecutive twenty-four hour urine collections totaling more than 120 individual specimens. All figures are expressed in mg. of creatinine per kg. of body weight in twenty-four hours. The figures for creatinine ex-

TABLE 1

Creatine and creatinine studies in monkeys

NO.	SEX	URINARY EXCRETION DURING NORMAL DIET			URINARY EXCRETION DURING VITAMIN E DEFICIENT DIET			DURATION OF DEFICIENCY BEFORE START OF OBSERVATION		REMARKS
		No. of det.	Creatine	Creatinine	No. of det.	Creatine	Creatinine	Months	Weeks	
			mg. per kg. per day	*mg. per kg. per day*		*mg. per kg. per day*	*mg. per kg. per day*			
47	M	8	4.8	36.8						
10	M	6	1.3	34.3						
12	M	20	3.8	39.5	5	*15.2*	36.3		2	Diet also vitamin C and calcium deficient.
					5	4.8	39.1		3	Diet also calcium deficient.
					13	1.5	41.8	1		Diet also vitamin C and calcium deficient.
					5	*22.5*	29.5	4	2	Intestinal upset.
					3	2.4	29.5	5	3	
5	M				9	1.6	18.0	11	2	
8	M				8	*7.0*	22.8	6	1	
					7	5.9	31.0	8	3	Diet also calcium deficient.
					11	*8.7*	24.7	15		
13	F	6	4.2	46.3						
14	F	3	1.6	38.5						
11	F	3	4.8	35.0	3	1.3	34.6	3		
10	F				3	1.4	36.5	13	3	
					3	3.8	31.6	15		
					4	*21.7*	28.1	16		
					4	2.6	26.8	16	2	

cretion range from 34 to 39 mg. for normal male and from 35 to 46 mg. for normal female monkeys. These amounts are definitely higher than in humans (cf. Hunter (10)).

The creatine varied form 1.3 to 4.8 mg. per kg. per day in both sexes, values which likewise surpass corresponding figures in human metabolism.

In the tocopherol deficient animals the creatinine excretion remained practically within the normal range. It varied from 18 to 41.8 mg. for the males and from 26.8 to 36.5 mg. for the females.

In three out of five deficient animals the daily creatine excretion was considerably elevated during at least one period of observation (italicized in table 1). The case of monkey number 12 was complicated by the fact that, before the final vitamin E deficient formula was applied, the diet used for this monkey was simultaneously lacking vitamin C and calcium. Upon addition of ascorbic acid the general condition of this animal improved and the creatinuria dropped back to the normal range; it only became elevated again for a few days during a temporary intestinal upset. The Java monkey (number 8) showed certain neurological symptoms (fibrillation of the tongue and the extremities) for a short period. Three months later when creatine excretion studies were begun, he showed moderately elevated creatine under prolonged observation.

From these experiments it appears likely that creatinuria may be produced in monkeys as a result of tocopherol deficiency. Like the neurological symptoms due to vitamin E deprivation this metabolic response is not as regular in monkeys as reported in other species. Experiments are in progress to determine the effects of tocopherol administration following the establishment of deficiency symptoms.

Similarity of symptoms had led to a number of attempts to correlate experimental tocopherol deficiency in animals with certain muscular and neuromuscular diseases in man and to treat such conditions with tocopherol. Bicknell (1) and Wechsler (20) described the effects of vitamin E adminstration in progressive muscular dystropy and amyotrophic lateral sclerosis and reported clinical improvement. Milhorat, Weber, and Toscani (12) likewise observed clinical improvement and diminution of creatinuria in two cases of dermatomyositis, whereas Fleischmann (5) reported no change in creatinuria or creatine tolerance in two cases of progressive muscular dystrophy and in one case of amyotonia congenita.

A series of patients with amyotrophic lateral sclerosis under tocopherol treatment offered an opportunity for the study of creatine and creatinine metabolism in this condition. Twenty-four hour urinary excretion of creatine and creatinine was determined in twenty-two patients and creatine tolerance tests were carried out in eighteen cases of this group.

Technique. Creatine and creatinine excretion in the urine was evaluated with the picric acid reagent of Folin (6) but we replaced the visual colorimeter by the Klett-Summerson photoelectric colorimeter using a green filter number 54 (transmission limits 520-580 millimicrons) and a solution depth of 2.5 mm. obtained by means of a reduction plate in the 10 mm. cell.

The excretion in fourteen male and six female subjects was observed during tocopherol treatment with a daily dosage varying from 100 to 750 mg. Seven of these patients (one female) were studied with and without vitamin E therapy, while two subjects (one female) were not treated at all. The figures given in tables 2 and 3 as mg. creatine and creatinine per kg. of body weight per 24 hour excretion are means over periods of varying lengths, averaging nine twenty-four hour urine collections. The patients were on an adequate mixed diet except during the creatine tolerance test. Their creatinine excretion ranged

from 9.3 to 27.3 mg. in the males and from 7.6 to 22.0 mg. in the females. The total averages of 17.7 and 18.3 mg. per kg. per day fell within the normal range. Though bedridden patients sometimes display moderate creatinuria, the excretion of creatine was definitely elevated in most cases. Healthy male subjects excrete no creatine at all, and healthy females with an average body weight of 50 kg. normally excrete less than 100 mg. of creatine daily, i.e., 2 mg. or less per kg.

TABLE 2

Creatine and creatinine studies in male patients with amyotrophic lateral sclerosis

NO.	AGE	URINARY EXCRETION DURING TOCOPHEROL TREATMENT			URINARY EXCRETION WITHOUT TOCOPHEROL TREATMENT			CREATINE TOLERANCE TEST—PER CENT RETENTION
		No. of det.	Creatine	Creatinine	No. of det.	Creatine	Creatinine	
			mg. per kg. per day	*mg. per kg. per day*		*mg. per kg. per day*	*mg. per kg. per day*	
1	37	24	9.2	18.0				86
2	41	27	5.4	13.9				
3	55	6	4.8	21.0	3	1.3	22.0	58
4	40	4	4.5	12.6				
5	50	12	3.4	16.6				79
6	46	16	3.0	13.9				94
7	38	8	2.4	18.0				
8	32	21	2.2	20.0	4	2.0	20.0	84
9	39	4	1.8	18.1	4	0.7	18.2	74
10	47	2	1.6	11.4	3	1.5	17.1	39
11	43	2	1.4	20.6				84
12	54	1	1.4	13.0	3	0.7	9.3	80
13	38	1	0.7	27.3				94
14	50	3	0.4	23.4	3	2.3	22.3	74
15	48				5	1.6	17.5	72

TABLE 3

Creatine and creatinine studies in female patients with amyotrophic lateral sclerosis

NO.	AGE	URINARY EXCRETION DURING TOCOPHEROL TREATMENT			URINARY EXCRETION WITHOUT TOCOPHEROL TREATMENT			CREATINE TOLERANCE TEST—PER CENT RETENTION
		No. of det.	Creatine	Creatinine	No. of det.	Creatine	Creatinine	
			mg. per kg. per day	*mg. per kg. per day*		*mg. per kg. per day*	*mg. per kg. per day*	
51	58	4	4.8	17.3	2	7.6	22.0	60
52	28	2	4.1	19.5				53
53	17	6	4.1	16.4				
54	58	9	2.3	7.6				86
55	48	7	1.8	18.8				88
56	50	3	1.2	9.4				85
57	37				3	0.8	21.3	

Table 2 does not show the unexplained fluctuations as observed in the creatine excretion of patients number 1, 2, 3, and 6. Their daily excretion which was

relatively low at the time tocopherol therapy was started, i.e., about 150 mg. per 24 hours, rose sharply two to four weeks after institution of the therapy. The excretion dropped again after several weeks of treatment, but remained distinctly above the initial level. There was no correlation between this extreme creatinuria and the clinical course.

Creatine tolerance tests were carried out, as described by Shorr, Richardson and Wolff (15) and Sohval, King and Reiner (16) before tocopherol therapy was initiated. Two out of fifteen males and two out of seven females showed retention of less than 70 per cent. Only in cases number 3 and number 51 did this abnormally low creatine retention coincide with high creatinuria.

Our observations of creatine and creatinine excretion and creatine tolerance during control periods when no tocopherol was administered, and the studies on untreated patients were limited by extrinsic factors, yet the results obtained warrant the statement that the creatine metabolism of these patients remained unaffected by tocopherol administration.

SUMMARY

1. Creatinine excretion was not affected by tocopherol withdrawal in monkeys; nor did it deviate from the normal range in patients with amyotrophic lateral sclerosis with and without tocopherol treatment.

2. Creatine excretion was elevated in three out of five vitamin E deficient monkeys, but this response, like the appearance of neurological symptoms, is not as regularly evoked in monkeys as in other species.

3. Creatinuria in patients with amyotrophic lateral sclerosis was elevated, and showed noticeable fluctuations.

4. The creatine tolerance test showed abnormally low retention in only four out of twenty-two cases of amyotrophic lateral sclerosis.

5. The creatine metabolism of patients with amyotrophic lateral sclerosis showed no correlation with the clinical fluctuation during tocopherol administration.

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THE DEVELOPMENT OF NEUROLOGICAL SURGERY IN NEW YORK CITY DURING THE PAST TWENTY-FIVE YEARS[1]

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There have been few who can look back upon so many years of accomplishment as can Bernard Sachs. It is a pleasure to greet him, hale and vigorous at more than four score years, and an honor to join in expressing homage to him in this Anniversary Volume.

Indirectly if not directly Dr. Sachs has had no little influence upon the development of neurological surgery in New York City. Through his energy and influence special wards for patients suffering from diseases of the nervous system were founded at The Mount Sinai Hospital. These were the first special wards for neurological patients in any New York hospital, and this made possible the growth and development of surgery of the nervous system in our institution.

In our country neurological surgery began to be a specialized field more than twenty-five years ago. I believe that some of the earliest operations for tumor of the brain, in New York City, were performed by Arpad Gerster at The Mount Sinai Hospital, by Charles McBurney at Roosevelt Hospital and by Andrew J. McCosh at the Presbyterian Hospital. In 1892, Frank Hartley independently described the operation for the intracranial exposure of the Gasserian ganglion, which procedure was for many years known as the Hartley-Krause operation, and in 1903, Robert Abbe, surgeon to St. Luke's Hospital, gave an account of the operation of "neurectomy" of the intracranial branches of the trigeminal nerve.[2]

For the development of the special field of neurological surgery a process of education was necessary, education not only of the neurologist but also of the general surgeon, the general practitioner, the laity and finally and most important of the neurological surgeon himself. Thirty or forty years ago, the neurologist found it necessary to call in a general surgeon when in rare instances an operation upon the central nervous system was deemed necessary. It was not surprising, therefore, that for many years the neurologist had the viewpoint expressed for example by Dr. Mills of Philadelphia seventeen years ago, that "one

[1] This paper was used in part for an address at a dinner held to commemorate the 25th anniversary of the organization of a neurological service at Bellevue Hospital, and was also read at a meeting of the New York Neurological Society in March, 1942.

[2] However, almost 300 years ago, the general surgeons of old New Amsterdam laid claim to the right to perform one type of "cranial operation." In the old Dutch records of New Amsterdam there is to be found the following note of the City Council: "Petition of the chirurgeons of New Amsterdam that none but they be allowed to shave." The action taken was: "The Director and Council understand that shaving appertains exclusively to surgery, but no man can be prevented from operating upon himself nor to do to another this friendly act, provided it is through courtesy and not for gain which is hereby forbidden."

of the functions of the neurologist is to superintend and direct operative procedures upon the brain and spinal cord by the surgeon." At about the same period, a similar view was expressed to me in writing by another eminent neurologist: "that the function of the surgeon was to do the technical work and to make the the opening in the skull or spine in the area mapped out by the neurologist, and that the surgeon should not attempt to make either a diagnosis or to localize the growth." In other words the surgeon was to be limited to his saw and chisel and was not expected to use his brains! *Tempora mutantur et nos mutamur in illis.*

As I have already stated, the emergence of neurosurgery as a specialty was the result of a process of education. Today we take it for granted that the technique and instrumentarium for operations upon the central nervous system are highly specialized, and that the operating personnel, both assistants and nurses, should be specially trained in order to be able to assist properly. Not so many years ago this was not generally acknowledged. While the writer was in charge of neurological surgery at The Mount Sinai Hospital, several years elapsed before he was able to convince a most capable hospital superintendent and Board of Trustees (not to mention his surgical colleagues) that a specially trained operating nurse was necessary, that a specially outfitted operating room was advisable and even that gray materials (towels, sheets, gowns, etc.) were an advantage. "You have central vision" they said, "an operation upon the brain is not different from any other operation as far assistants and materials are concerned."

During the many years that passed before neurological surgery was accepted as a specialty, various influences were at work. Knowledge of the localization of functions in the brain and spinal cord was being steadily advanced. Some young general surgeons began to devote themselves to operations on the nervous system, and what was of no little importance, they gained increased knowledge of the symptoms and diagnosis of diseases of the nervous system. The general surgeon gradually appreciated that these operations had best be done by those who had gained a large experience in this branch of surgery. *Pari passu*, the neurologist learned that only the surgeon who had gained a large experience with these operations should be asked to perform them; the general practitioner began to learn the same fact, and the laymen commenced to expect that patients who required an operation upon the central nervous system should be referred to the surgeon who was specially trained in this field. It is a lasting credit to American Medicine that the accomplishment was due to the efforts of a small number of surgeons of our country among whom Harvey Cushing must be especially mentioned.

Until recently neurological surgery was a specialty only in the United States. There were many surgeons in this country who limited themselves to operations on the nervous system at a time when there was practically no worker abroad who thus limited himself. In Great Britain, in spite of the influence of Victor Horsley and of the Hospital for Paralyzed and Epileptic in London, neurological surgery was not a specialty for many years. About twenty years ago, Percy

Sargent, who succeeded Sir Victor Horsley in charge of surgery at the hospital in Queen's Square in London, said to me that he did not believe that there was a sufficient number of patients with tumors of the brain in London who would be referred by their physicians to a "neurosurgeon", to give the surgeon enough to do! In France, the lamented De Martel, although he was a skillful operator on the brain and spinal cord, remained a general surgeon to the end of his life. He was greatly impressed by American neurosurgery, often visited us and used American methods. He prepared the field for Clovis Vincent, Petit Dutaillis, Paul Martin and others. Even today there are few neurological surgeons in Germany or Italy, although many years ago Fedor Krause in Berlin and Raffaele Bastinelli in Rome did considerable surgery on the central nervous system.

In order that a neurosurgical service may be developed in a general hospital, the administration must be able and willing to provide the necessary apparatus and instruments and the trained nurses and assistants for the surgeon. As is obvious, a capable operating team cannot be developed in an institution in which a major operation upon the central nervous system is performed only a few times a year. For this reason, a neurosurgical service can be developed only in a special hospital or in a general hospital in which there are special neurological wards. In most of the general hospitals in New York City, until about twenty-five years ago, there was not a sufficient number of patients to justify a special neurosurgical service. If the Neurological Institute be excepted, there were active neurological surgical services only at The Mount Sinai Hospital and at Bellevue Hospital, in both of which institutions there were special neurological wards. Recently, departments for the surgical treatment of diseases of the nervous system have been developed in the Brooklyn Jewish Hospital and the New York Hospital.

It was logical that neurological surgery should have first developed as a branch of general surgery. Dr. Cushing, Dr. Frazier and the writer all had a not inconsiderable experience in general surgery before they began to devote themselves to operations on the nervous system. There is perhaps a certain disadvantage in what is happening today, that after their internship, young men receive their training in neurological surgery and become specialists in that field without having had a good basic experience in general surgery. A neurological surgeon may be developed in one of three ways: 1) a general surgeon may devote himself to neurology and gradually limit himself to operations on the nervous system; 2) a neurologist may learn to do his own operating; 3) a neurosurgeon may be born full fledged from an assistant as Minerva was born fully developed from the head of Jupiter. A few neurologists without much previous experience in surgery have learned to operate upon their own patients, as did the late Ottfried Foerster and Clovis Vincent, some specially talented men have become skillful neurological surgeons without having had a preceding experience in general surgery, but all in all I believe that a basic experience in general surgery is very advisable.

As the neurological surgeon became a better neurologist he was no longer looked upon as merely a technician; he was consulted for his opinion as to

diagnosis and localization of an intracranial or spinal lesion as well as to perform an operation if such was required. This is perhaps shown by the number of neurological surgeons who have, in recent years, been elected to membership in the American Neurological Association. Twenty-five years ago, in 1916, there were 121 active members in the society of whom 5 (4 per cent) were neurosurgeons; in 1925, there were 8 neurosurgeons among 149 members (5 per cent); in 1935, 10 of 165 active members (11 per cent), and in 1940, 27 of 191 active members (14 per cent). The steady increase in the number of neurological surgeons in the American Neurological Association was a cause for perturbation of some members. One of the members wrote to the Council of the Association and asked how long it would be, at the same rate of increase, before the American Neurological Association would consist mainly of neurological surgeons!

I have wandered far afield and somewhat away from the story of the development of neurological surgery in New York City. As soon as a few centers for the surgery of the nervous system had been developed, a number of young men were trained in this specialized field. They either continued to work in the institution in which they had received their training or they received appointments in other hospitals in New York City or elsewhere. At the close of the First World War, there were a few men who began to practice neurological surgery after their experiences with injuries of the brain, spinal cord and peripheral nerves in that conflict. However, to a considerable extent, a broader experience is necessary for the practice of neurological surgery in civil life.

Soon after the beginning of the period concerning which I am writing, neurosurgery was accepted as a specialty. This is shown by the fact that about twenty-one years ago, Columbia University, at the College of Physicians and Surgeons, established a full chair of neurological surgery with a seat on the faculty of the Medical School.

During the past twenty-five years, there have been twenty-three neurological surgeons connected with the various hospitals of New York City. Of this number, the experience of two was that gained in the First World War, while the others had either received a thorough training in one of our institutions or in a neurosurgical clinic in some other city. One of these was a woman, Dr. Dorothy Klenke. At the present time there are sixteen men in the Greater City who devote themselves entirely to neurological surgery and several younger men who are beginning to do so. Of the twenty-three surgeons who have practiced the specialty in New York City, two have retired, three have moved to other cities, and two have died, Dr. James H. Kenyon and Dr. Earl D. Brewer. Dr. Kenyon died in middle age and Dr. Brewer, a man of unusual promise, died at the age of thirty-two.

During the first years of the twenty-five year period, most of the neurological surgery done in New York City was, naturally, done at the Neurological Institute which was a special hospital, and at The Mount Sinai Hospital in which there were special wards for patients suffering from diseases of the nervous system. However, as soon as special wards for neurology were founded at Bellevue Hospital, an active neurosurgical service developed at that institution. The service at Bellevue was first in charge of Dr. Alfred S. Taylor and the surgery

was done by Dr. Taylor, Dr. J. J. King, Dr. Byron Stookey, Dr. Klenke, and later by Dr. Scarff and most recently by Dr. Pool. At the Neurological Institute the surgical staff was headed in succession by Dr. Elsberg, then by Dr. Stookey and now by Dr. Tracy Putnam, and operations were also performed by other neurosurgical staff members: Drs. Alfred S. Taylor, Wilder Penfield, Kenyon, Davidoff, Masson, Deery, Klenke, Cramer, Brewer, and later by Dr. Scarff. At The Mount Sinai Hospital, the neurosurgeons were the writer and Dr. Ira Cohen, and after Dr. Elsberg's resignation, Dr. Cohen, Dr. Kaplan and Dr. Gross. Three neurological surgeons work in Brooklyn, Drs. Davidoff, Jefferson Browder and Anatole Kolodny. At the Polyclinic Hospital, some neurosurgery has been done by Drs. Sharpe and Ney. Recently a neurosurgical service has been developed at New York Hospital by Dr. Bronson Ray. A few years ago, an effort was made to have a special neurosurgical service at the Post-Graduate Hospital but the material was not sufficient and the active heads soon resigned.

If I may now turn to a recital of some of the contributions of New York neurological surgeons, I want first of all to mention Dr. Alfred S. Taylor. He developed the technique of operations for birth paralysis of the nerves of the brachial plexus and, independently of two Italian surgeons Alessandri and Bonome, who had described the operation before him, devised the procedure of unilateral or hemilaminectomy. I think that Dr. Taylor's contribution to the technique of the operation of unilateral laminectomy and the instruments he devised for the procedure will last.

It is fair to state that the development of spinal cord surgery was due to a great extent to the work of New York neurosurgeons; they made contributions not only to the technique of laminectomy but also to the clinical features and the diagnosis of tumors and other lesions of the spinal cord, membranes and nerve roots. Also, I believe that in this country, the first craniotomies that were done under local infiltration anesthesia were performed at the New York Neurological Institute soon after local anesthesia for this purpose had been recommended by Dr. DeMartel of Paris.

Another operative procedure in the development of which New York neurological surgeons played a part was the differential section of the posterior root of the trigeminal nerve for neuralgia. Credit for the development of the exact technique of this operation should be shared by the late Dr. Charles H. Frazier of Philadelphia who performed the first of these operations, by Dr. A. W. Adson of Rochester, Minnesota, and by Dr. Byron Stookey of New York City.

I have mentioned only a few examples of the many contributions to neurology and neurological surgery by New York surgeons, but there is hardly a single worker in this branch of surgery that has not made an important contribution. Many new operative procedures were devised by them and clinical syndromes described. Thus one might mention giant tumors and radiculitis of the roots of the cauda equina, Davidoff-Dyke-Masson disease, extradural spinal cysts, meningiomas of the mesial part of the sphenoid ridge, the improved methods for the determination of spinal subarachnoid block, the treatment of abscess of the brain, etc.

Advances in neurological surgery have been closely connected with the develop-

ment of the roentgen diagnosis of intracranial and spinal diseases and here also New York neurosurgeons have played an important part. Great advances have been made in our knowledge of the pneumographic appearance of the normal cerebral structures, and of the characteristic changes seen in the ventriculogram and encephalogram in tumors and other intracranial lesions. The characteristic alterations seen on roentgen films of the spine in spinal cord tumors, and the changes in the pedicles of the vertebrae in spinal diseases and the significance of interpediculate measurements were first described by a New York surgeon together with a roentgenologist, Dr. Cornelius G. Dyke.

Finally, one may ask: What of the future? That old Roman Cicero said, "in no function do human beings approximate the gods more closely than in bestowing health upon their fellowmen." The object of our therapeutic efforts, of both neurologists and neurological surgeons, is to benefit our patients. We change our methods or endeavor to improve them as soon as we realize that we are accomplishing little or nothing. But the road is often long and difficult. There are some diseases of the nervous system for which surgery has been unable to do much or only to palliate and for the treatment of which other methods will have to be found. Thus, it seems probable that when in the future the preoperative diagnosis can be made with more certainty, fewer operations will be performed for the malignant tumor called glioblastoma multiforme, and that the future treatment of the growth (if it is a true newgrowth and not a glial reaction to some noxious agent) will be radiologic or perhaps serologic. Likewise, in purulent infection of the meninges, future therapy will not be surgical. Is it going too far for me to express the suspicion that in the years to come, operations in which nerves or nerve tracts are now being divided, will become more rare? We are doing the best we can today, but will the diseases be treated differently in the future? I think so! The isolation and synthesis of many of the vitamins by the biochemists have opened up a large field for clinical investigation, and "these discoveries of the biochemists if applied to the prevention and treatment of diseases of the nervous system, may be compared in importance to the discoveries in bacteriology made forty to fifty years ago!"

How fortunate are we of this generation to have seen the great advances in neurology and neurological surgery during the past twenty-five years! How humble we must feel when we appreciate that the human brain must still be in an early state of its development if a world cataclysm evolved by human or inhuman minds and with human knowledge can still engulf us!

INTERRELATION OF ESTROGENS AND THE NERVOUS SYSTEM

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In the course of evolution, humeral integration of the organism antedated nervous control. Yet nervous mastery developed so strikingly and obviously, that, not until the new science of endocrinology had matured, was the full significance of the internal secretions upon effector organs recognized. Today we are aware of the intimate correlation and interplay of nervous and endocrine mechanisms to an extent which justifies the dictum that peripheral control of the autonomic nervous system in part is a hormonal function. This interrelationship is in no way confined to the autonomic nervous system; it embraces the higher levels, the bulbar and spinal centers, as well as the organs of the special senses.

This presentation is limited, in the main, to the effect produced by one of the female sex hormones, the estrogen group, upon the nervous system and the resultant physiologic and pathologic manifestations resulting therefrom.

Endocrine secretions, however, can produce changes on the effector organs without the intermediation of any nervous mechanism. This is proved by the simple experiment of transplanting uterine tissue, both muscular and glandular, to a new site, and, after a time sufficient to allow for the degeneration of possible end organs as well as all other nervous structures has elapsed, to administer estrogen to the experimental animal. The response of both uterine muscle and endometrium is identical with that obtained in the untransplanted organ (26).

Unfortunately in dealing both with experimental animals as well as with human beings, few equally clearcut demonstrations of either endocrine or nervous function can be devised. Nor are we at present in a position to analyze clearly all of the interesting problems which confront the clinician. An attempt to survey even cursorily, the cerebral, subcerebral and peripheral actions of these systems, may be premature. Nevertheless it is a tempting undertaking. Unquestionably frequent revision will be needed as new data accumulate.

CEREBRAL EFFECTS

In the lower animals, particularly in the laboratory rodents which have been most closely studied, castration produces a measurable diminution of spontaneous activity. Both male and female human castrates note an increased feeling of well being, physical and mental, after receiving respectively male or female sex hormones in adequate quantities. As yet these reports are based upon subjective statements and, therefore, are not measurable. Abolition of interest in the opposite sex develops in castrate animals. This is due to the removal of the sex glands with consequent deprivation of the sex hormones. Even under these conditions, an additional complicating factor must be reckoned with, in that castration causes an increase in hypophyseal gonadotropic secre-

tion, (16) possibly an increase of other hypophyseal factors as well. Nor should one forget that "The induction of mating behavior in female mammals" as analyzed by Young (48) in his excellent review, ". . . is the result of very complex processes. The interaction of endocrine, neural, genetic, ontogenetic, nutritional, environmental, psychological, pathological and age factors is known to be involved and doubtless others are important." Even more discouraging is the situation when we turn to the primates among whom we must include *homo sapiens*. In animals below this general group, the male is accepted only during estrus. In primates and particularly in the human, the sexual act is performed irrespective of the cycle, in the human little if any trace of sex season surviving. Castration in the human female, rarely depresses libido. In the human female both libido and frigidity are not influenced convincingly by injection of large doses of estrogens. The validity of this observation is weakened somewhat by the fact that in the castrated human male, testosterone, the male sex hormone, temporarily restores sex desire and *potentia coendi*. This seeming difference may be accounted for by the fact that although in both sexes mating behavior is integrated by the hypothalamus (7), in the human female cerebral control, especially inhibitory, plays a greater role.

Clinically at least there is much evidence that in the vast majority of human females, such manifestations as frigidity and dyspareunia are not of local origin, but the result of cerebral inhibitions due to aversions, compulsions and other results of maleducation or mismating. This view is strongly fortified by the ineffectiveness of estrogenic injections for frigidity and the lack of success of local measures in overcoming dyspareunia. On the other hand, both of these symptoms may be alleviated or cured by enlightenment, if mild and of short duration, or by analysis in the graver forms.

In order to present both sides of the question, it should not be forgotten that a condition well known to veterinarians, called, perhaps mistakenly, "nymphomania" is noted in cows. In these animals, persistent and exaggerated ovarian follicle development is observed in the ovaries. The animals are restless, mount other animals indiscriminately, bellow, show exaggerated sex excitation over long periods. The condition is cured by bilateral oophorectomy, and is associated with an overproduction of estrogens by the too numerous and persisting follicles (47).

It may be stated that no convincing evidence has been offered that human homosexuality is due to endocrine changes. It is true that no large and well controlled groups have as yet been studied. Various degrees of homosexual activity are manifested among the lower mammals (see Young). At present certainly the concept of a psychic basis for this aberation seems a justifiable conclusion as applied to the human.

Recently much interest has been aroused by the report of the good effects of estrogens upon psychoses developing at the menopause (25, 45). My own impression, based mainly upon a detailed study of the published reports, is that milder symptoms, such as transient fears, anxieties, and unrest are benefited, coincidentally with the reduction of climacteric neurovascular disturbances.

I am not convinced that the deeper seated disturbances are alleviated. Others appear to be coming to this same conclusion (Ripley, Shorr and Papanicolaou (38)). Latent or impending psychoses not infrequently are activated by the discomforts originating from and the fears associated in the minds of the laity with the onset of the climax.

Evidence that the higher centers are affected by the sex hormones is offered by the psychical changes which occur in both males and females at puberty. Endocrinologically this epoch manifests itself by an increase in the secretion of both the male and female sex hormones (34). Such manifestations as the development of pudor, timidity, assertiveness, etc., must be ascribed to hormonal influence upon the psyche. In adolescents afflicted with hypogonadism, a low secretory level of sex hormones persists, and the expected psychical changes fail to develop in this age group.

The menstrual sex cycle results from complicated hormonal variations in the blood. Of these variations, some are qualitative as the chronologically limited secretion of the corpus luteum—twelfth to twenty-third day (42); others are quantitative, as the fluctuation in concentration of gonadotropic-prepituitary and estrogenic factors throughout the cycle (17, 19). It is known that at the time of menstruation, marked transitory character changes and demeanor alterations occur in a not inconsiderable number of otherwise normal women. Mild symptoms such as irritability, increased mental fatigability, lack of self-control, are regarded as physiological. There is a smaller group in whom melancholic incidents, suicidal tendencies, mild and even grave criminal impulses manifest themselves and are strictly limited to this time. These psychical variations appear directly due to hormonal influences.

This concept is confirmed by a small group of cases which I have called "premenstrual tension" (18). Hormonal investigation showed that, premenstrually, an abnormal, assayable increase of estrogen accumulated in the blood of these individuals. As soon as they menstruated, the blood titer diminished abruptly, the symptoms disappearing simultaneously. In this group alone, of all of the thousands of non-pregnant women on whom blood assays have been performed, did the estrogenic blood titer mount to such a high level. During pregnancy in which a much greater estrogenic blood titer is physiologic, this increase is accompanied by so many other dramatic hormonal changes that a protective mechanism may develop.

Spaying is said to increase not only the body, but also the brain weight of female rats; castration of males on the contrary decreasing both factors. The same applies to the quantitative figures for the different chemical compounds of the brain. Qualitatively an increase in the phosphorus in alcoholic extracts of the brain is noted in females after oophorectomy (43). The neurologic or endocrine significance of these observations is as yet unknown.

An interesting but uncommon syndrome is the occurrence of epileptic seizures strictly limited to the premenstruum. Caution must be exercised in assigning a patient to this group. In the majority of instances, detailed history taking will show that seizures are more frequent at the time of the menses, but also

take place in other phases of the cycle. Such individuals must be excluded. However, I have encountered two clearcut premenstrual epileptics without localizing symptoms, both women under twenty-five years of age. In both, sterilizing doses of x-ray were given. In the one, no improvement ensued. In the other, a complete cessation of the attacks resulted for two years; then out of a clear sky a seizure took place, followed in four weeks by a normal menstruation. X-ray treatment was repeated; the menses thereupon permanently abolished. Since then no further attacks have occurred. And yet, in the light of recent investigations, the explanation may not depend upon a direct action upon the nervous tissues. Thorn (40) has shown that premenstrually an increase of adrenocortical secretion is noted, with resultant retention of electrolytes and consequent development of edema, sometimes widespread, sometimes localized. Such an intracerebral chemical edema (32), if localized, could well induce an epileptic seizure.

Far less analyzable are the effects produced by the higher centers upon the sex organs. While we are familiar with the reports of amenorrhea produced by shock, profound grief, fear of pregnancy, as yet such effects have not been explained convincingly. Kuntz (27) states that no sustainable evidence, that any of the visceral organs are subject to direct cortical influences, has been presented.

Yet Bard (1) has shown that the central nervous mechanism profoundly influences emotional behavior patterns in animals. His researches have established that estrual behavior, for example, depends on the presence of certain hormones in the blood and that the central integrating mechanism concerned "must be under the direct or indirect influence of specific chemical substances." The endocrine domination of these impulses is proved by the fact that after removal of the olfactory stalk, as well as the severance of connections which conduct visual and auditory impulses, there is no diminution in mating activity and subsequent ovulation as long as the necessary hormonal conditions persist (8). In spite of this dominance, psychical impotence in the male is of common occurrence and unaccompanied by azospermia.

On the other hand, as Britt (6) has shown, the daily blowing of motor horns or air jet noises, shorten the sex cycle in rats. This effect was abolished by the removal of the cervical and lumbo-abdominal sympathectomy which may mean that these results are due to autonomic rather than direct cerebral influence. Apparently minor stimuli may likewise influence the periodicity of the sex cycle. Many years ago, in a personal communication, Leo Loeb called my attention to his observation that in regularly cyclical guinea pigs observed for many cycles, the cycle might be interrupted for weeks if these apparently stolid animals were handled by a strange attendant. I have repeatedly convinced myself of the accuracy of this observation.

DIENCEPHALON

The diencephalon harbors vegetative centers of maximum importance. These include centers governing the general metabolism, the metabolism of water, of carbohydrates, body temperature, blood pressure as well as sexual reflexes.

The preponderance of evidence favors the view that at least some of the endocrine glands respond to excitory or inhibitory nervous stimuli originating in the diencephalon (adrenal medulla, anterior and posterior pituitary). In attempting to analyze such nervous influences, complex situations are encountered. Special caution must be exercised in attempting to apply to human beings the result of experimental observations obtained from animals in the hypothalamic area. For as Fulton (21) has so aptly phrased, "There is a progressive encephalization of autonomic control as one ascends the evolutionary scale, and it is probable that the relative simplicity of the hypothalamus in man and anthropoids, as compared with the lower vertebrates, reflects the increasing dominance of the cortex in this aspect of autonomic regulation."

There is conclusive evidence that an adenohypophyseal—ovarian endocrine interrelationship exists. Gonadotropic pituitary factors, whether of gland or chorionic derivation, induce ovulation and luteinization in the infantile rodent ovary. After hypophysectomy, the same response usually can be elicited, but at a much higher dosage level, the required dosage being at least eight times above that effective in the intact animal. This might indicate a purely endocrine action were it not for the fact that in certain rodents the condition of pseudopregnancy (in which secreting corpora lutea persist as in true pregnancy) may be induced experimentally by tactile stimulation of the utero-cervical canal (31). This reaction fails if the hypophyseal stalk has been severed without in any way disturbing the adenohypophysis. Furthermore, pseudopregnancy may be induced in rodents by stimulation of the nasal mucosa or removal of the sphenopalatine ganglion (39). Nervous connections between the nasal mucosa, through the sphenopalatine ganglia have been traced into the substance of the hypophysis (49). All of the nervous pathways are as yet not known. Hypophyseal stalk section, although it severs the numerous fibers which run from the neurohypophysis to the nucleus supra orbitalis, does not block the pathway of fibers from the nasal mucosa and sphenopalatine ganglia which reach the hypophysis by following the numerous blood vessels arising from the internal carotid.

Further evidence of a diencephalic influence is shown by the following. Ovulation may be induced in estrous rabbits by subthreshold doses of gonadotropic factors injected intravenously if activated by such chemicals as copper acetate, cadmium salts, metrazol or picrotoxin. This reaction was interpreted by Fevold et al. (15) to an increase of effective activity of the gonadotropic factors by the copper. Harris (23), however, has found that $\frac{1}{200}$ or even $\frac{1}{300}$ of the amount of copper acetate needed for intravenous injections, when injected alone directly into the third ventricle, causes this same reaction. This he interprets as a proof of direct chemical action upon the hypothalamus which thereupon initiates ovulation, doubtless through the mediation of the hypophysis. Analysis of these results is neither simple nor unequivocal for Friedman (20) with progestin, blocked the copper effect but did not influence the gonadotropic threshold.

In this connection the clinical observation that pineal tumors may produce pubertas praecox is germane. This usually has been interpreted as the effect

of an assumed endocrine secretion from the pineal. The experiments contained in the preceding paragraph, lend further weight to the more recent view (2) that pineal tumors produce sex effects by means of the pressure they exert upon the diencephalon and that the hypothalamic nuclei thereupon stimulate the adenohypophysis. The adenohypophysis justly has been called the puberty gland as its action directly initiates puberty by activation of the gonads. The entire train of symptoms when followed, starts with a pressure stimulus on the hypothalamus, subsequent stimulation of the adenohypophysis, particularly of its gonadotropic function, with consequent activation of the infantile ovary or testis. The peripheral effector organs are the tubular genital organs in both sexes. This important question deserves further investigation by experimental means.

The preceding has offered some explanation of excessive, prolonged, and premature sexual phenomena. The opposite conditions, that of retarded or suppressed development of the sex organs, unless accounted for by inherited factors, by severe malnutrition or wasting disease, remains even more obscure. Regression of the genital tract develops progressively in the rare condition of Simmond's disease, due to atrophy or destruction of the adenohypophysis. By actual experiment, it has been shown, on animals, that malnutrition quantitatively reduces the amount of hypophyseal gonadotropic secretion (44). That the adenohypophysis is influenced by many endocrine conditions is well known. Calling it the "master gland" is a misnomer, because of its dependence both upon other endocrine glands as well as upon nervous control. For example, Dey (14) noted the appearance of ovarian changes and sterility in guinea pigs following the production of hypothalamic lesions. These could only have been mediated through the adenohypophysis.

A well known syndrome, "anorexia nervosa," which more properly should have been discussed under cerebral effects, is presented here because, not infrequently, it has mislead experienced endocrinologists and neurologists. These patients are mistakenly classified as victims of Simmond's disease. The causation is psychical, resulting in profound malnutrition which in turn temporarily gravely reduces hypophyseal function, entailing a long train of symptoms. These cases are regularly cured by rest cures and psychotherapy.

The temptation arises to attempt to ascribe retardation of sex development to a combination of both neural and endocrine influences, but in the present state of our knowledge this would be extremely hazardous. No obvious explanation for the common clinical syndrome of "hypogonadism" has as yet been evolved. A large group of adolescents of both sexes, mature either incompletely or belatedly. Endocrinologists are inclined to ascribe the retardation to primary hypophyseal underfunction, but are unable in the majority of instances to find the etiological factor. Moreover, in my experience, the vast majority of these adolescents eventually mature, some without lasting stigmata, others permanently showing some marks of infantilism. Hereditary constitutional factors unquestionably play some role. For example, I have observed members of three generations of the same family, all tall, thin, with somewhat high pitched voices

and hairless faces, in whom one testicle failed to descend until the age of eighteen. I am loath to attribute this self-limited hypogonad syndrome, which should be classified as pseudo-Froehlich or pseudo-Levy-Lorraine types of pituitary hypofunction, to a primary endocrine disturbance until much further evidence has been offered, and yet I am unable to find any hypothalamic cause to account for the transient nature of the syndrome.

SPINAL

Our knowledge at these levels is too incomplete to warrant an attempt at analysis. In the male in whom the reaction is more clearcut than in the female, sacral cord centers mediate reflex erection by parasympathetic channels, and another at lumbar level which mediate ejaculation (sympathetic) (46). Castration prevents this reaction but both androgens and estrogens reestablish the ejaculation, which has been used by Loewe (30) as a hormone test. Herren and Haterius (24) state that the estrogens increase the length of the Achilles tendon reflex time as determined electro-myographically, but they believe that this should be ascribed to the heightened activity of the higher nervous centers such as the cerebral cortex. An observation of considerable interest is that of Van Wagenen (41) who found that transection of the spinal cord between the eighth and twelfth thoracic level in monkeys, when practiced in the earlier half of the cycle, was regularly followed in two to nine days by uterine bleeding. A normal cycle was later reestablished in these animals. Transection of the cord in a castrate produced no bleeding.

PERIPHERAL

On the sex organs of the female, which include the ovaries, the Fallopian tubes, the uterus and the vagina primarily; the breasts and secondary sex characters secondarily, hormonal control predominates. The transplanted ovaries and uterus, freed of all nervous connection, respond to appropriate hormonal stimuli and can undergo normal cyclical variations. The genital tract when denervated and separated from central control, can carry out its gestational function—ovulation, fecundation, pregnancy, labor and puerperal involution.

Yet is is inconceivable that the complex and elaborate nervous apparatus which leads to and encompasses the genital tract, does not subserve important functions, at least in intergrating these organs with the body as a whole. A wealth of literature dating back for more than one hundred years, deals with the pelvic nerves and innervation of the genital organs. Of this, only such as has immediate application to the present theme, can be considered.

Autonomic innervation reaches the uterus and proximal half of the Fallopian tubes through the hypogastric plexus situated in the midline at the promontory. These nerves are derived from the coeliac, the mesenteric and intramesenteric plexuses. The hypogastric fibers, together with branches from the second, third, fourth sacral nerves form the pelvic plexuses, lateral to the utero-cervical junction. The nerves from the pelvic plexus reach the uterus mainly through the sacro-uterine ligaments but also by accompanying the uterine arteries.

Vasoconstrictor fibers appear to accompany all the blood vessels which reach the genital tract from diverse directions. The ovaries and distal portion of the tubes are innervated by nerves accompanying the spermatic (ovarian) arteries.

The function of some of these nervous tracts have been clarified by animal investigation. The motor innervation to the whole uterus passes through the third, fourth, fifth lumbar ganglia of the lateral sympathetic chains (29). According to Reynolds (37), individually they innervate restricted sections of the musculature only, at least in the long bifid uterus of the rabbit. Whether this applies to the shorter single uterus of the human must remain an open question although studies upon the uterus of the fetus and neonatus show a similar distribution (9).

The sensory impulses from the uterus pass upward mainly, perhaps exclusively through the hypogastric plexus. Their further course has not been determined. Severance of the presacral hypogastric fibers arrest uterine sensation of pain. In the rabbit, no intrinsic ganglia are present in the uterus above the utero-cervical junction. The same appears to hold true for the human (9). This cannot be stated with any certainty for other species. Great variation in reaction to nerve stimulation is noted in the cat, rabbit, rat, dog, monkey and human.

This is well illustrated by the "pregnancy reversal" reaction. Stimulation of the hypogastric nerve produces relaxation of the uterus in the non-pregnant cat (12), contraction in the pregnant cat and rabbit. In the rat and guinea pig, adrenalin and nerve stimulation produces inhibition both in the pregnant and non-pregnant state (22). Labate (28), from the result of cocaine accentuation, believes that the "hypogastric nerves of the cat and rat are predominantly adrenergic, whereas in the rabbit and monkey the hypogastric nerves contain a relatively higher percentage of cholinergic elements."

This great variation in the innervation of such a phylogenetically old and indispensable organ system favors the view that the nervous system in this area is in a state of evolution and does not play a major functional role. Further evidence that endocrine secretion dominates is supplied by other observations.

In the mouse the pelvic plexus contains ganglia whose cells are chromophobic when deprived of estrogen, chromophilic under estrogenic influence (3).

In the rabbit "injection of estrogen is followed within an hour by an increase in the free acetylcholine content of the uterus" (35). This takes place also in transplanted uteri (26). In cats and rats estrogen is not cholinergic. Even in the rabbit this estrogen cholinergic augmentation is localized to the uterus and does not occur in skeletal muscle, intestine or spleen (36). Further examples illustrate the endocrine dominance and yet demonstrate the close interaction of endocrine and nervous phenomena. In the isolated anestrous uterus of the cat, response to electric shocks is local; in the estrous uterus, general. Moreover injection of estrogen produces an increase of electric excitability and in the resting potential (4).

These investigations give some insight of the control of the genital organs both

hormonal (dominant) and nervous (accessory). Yet these functions may play a decisive role in the process of reproduction and explain, in some measure, functional disturbances such as sterility and dysmenorrhea.

In the process of reproduction, accurate timing is indispensable. The survival period of the unfertilized ovum is limited—overripe ova produce malformation, monsters, fetal neoplasms (5). Conjunction of ovum and spermatozoon must be chronologically precise—too early, may result in ovarian pregnancy; delayed, may cause tubal gestation. Premature expulsion of the fertilized ovum from the tube into the as yet unsensitized uterus terminates in abortion. A disturbance of motility ("locking the tube") can be induced experimentally, as Burdick and Pincus (10) have shown, by injecting estrogen in excess. Progestin acts as a uterine relaxant and therefore reduces the strength and frequency of uterine contraction which otherwise might expel the ovum prematurely before it has penetrated into the endometrium.

Thus it would appear that nervous control plays but a minor rôle in the vital reproductive process, as, both under experimental and clinical conditions, impregnation and pregnancy have ensued, after all cerebral, spinal and autonomic pathways have been severed.

An insight into the nervous control of the uterus is afforded by the syndrome of dysmenorrhea. This manifests itself by the occurrence of pelvic and lower abdominal pain premenstrually and during the flow. The symptoms may appear at puberty and continue until the menopause. A majority of patients are permanently relieved by childbirth. Dysmenorrhea is more frequent in infantile individuals, in neurotics and in overworked adolescents. The evidence offered by Davis (13) of the presence of a neurileminal edema and ganglion changes in the region of the sacro-uterine ligaments is not too convincing. However, it may be analogous to the ganglion changes in the mouse, observed by Blotevogel et al. (*vide ante*) under the influence of estrogens. In virgins and uninfected married women, infection plays no role. Inflammation may account for the occurrence of so-called "secondary" dysmenorrhea which develops during and after pelvic inflammations.

The conduction pathway for both efferent and afferent impulses to the uterus are through the hypogastric plexus, those to the ovaries through the spermatic (ovarian) plexus (28*a*), as previously mentioned.

None of the many alleged etiologies of dysmenorrhea have stood the test of critical examination. This applies particularly to the supposed functional stenosis of the cervix for the relief of which dilatation and plastic operations were performed. That psychosomatic changes precede menstruation, reducing the threshold for pain, may be accepted. An ovarian etiology may be excluded because mechanical insults to the ovaries, as studied on the human individual, operated upon under local abdominal wall anesthesia, produce no pain. In the anesthetized cat, slight sensory response can be elicited experimentally by observing changes in the blood pressure and respiration. Also the operation introduced by Kelly many years ago and long since abandoned, of resection of the

nerves of the broad ligament for dysmenorrhea, proved futile. On the other hand, dysmenorrhea is abolished by hysterectomy although the ovaries are preserved.

Davis, who like most investigators, ascribes the origin of pain to unduly strong uterine contractions, considers dysmenorrhea analogous to intermittent claudication and angina pectoris. According to him, the pain is due to the muscle ischemia resulting from abnormally strong muscle spasm. Moir (33) claims that pain is produced as soon as the uterine pressure exceeds that of the manometric pressure in the brachial vessels.

Presacral sympathectomy as practiced by Leriche, Cotte, and many others, cures dysmenorrhea in the majority of patients. The operation proposed by Condamin (11), consisting of vaginal or abdominal severing of the uterosacral ligaments and posterior parametrium through which a majority of afferent fibers from the uterus run, to my knowledge has not been practiced. Its efficacy appears doubtful as numerous other fibers from the superior hypogastric plexus reach the uterus through other channels such as by accompanying the uterine vessels. Presacral sympathectomy, necessitating laparotomy, is a surgical intervention of some gravity. It interrupts not only the uterine innervation but also that to other of the pelvic organs (rectum, bladder). Consequently it has been reserved for the severest and most intractible cases.

The vast majority of patients suffering from dysmenorrhea have been treated medically with antispasmodics, combined with coal tar preparations. Atropine may afford relief. Progestin and its congener, pregneninolone, has also been given. The cocainization of the inferior turbinates of the nose, introduced by Fliess, followed by cauterization, which was first practiced on purely empiric grounds and which later has been based on a sounder foundation by the researches of Rosen et al. (*vide ante*) has likewise been used. None of these measures has proved fully satisfactory. As a rule, the relief is transient, extending over one or two periods, with failure thereafter. Consequently we must ascribe many of these temporary results to autosuggestion.

Castration cures dysmenorrhea by abolishing the menstrual cycle, but not by its direct effect on the ovaries. This is demonstrated if x-ray castration is utilized. In young women the dosage can be graduated to temporarily abolish the ovarian function (nine to twelve months). When the ovaries again resume their activity, prompt recurrence of the dysmenorrhea is the rule.

The permanent relief of dysmenorrhea by childbirth, which although not invariable, occurs in the vast majority of patients, conceivably might result from the prolonged and enormous increase in estrogenic and gonadotropic secretion, the consequent hyperplasia of the musculature as well as in the prolonged pelvic turgescence accompanying pregnancy. Usually it has been ascribed to the overdistention of the cervical segment in which numerous ganglia are located. Some investigators prescribe large doses of estrogen for dysmenorrhea with the object of producing uterine muscle hyperplasia. All in all, the therapy, unless radical, and this is indicated rarely, has proved disappointing.

As previously mentioned, neither frigidity nor dyspareunia should be ascribed to local causes. Their causation appears to be cortical.

It would be premature to attempt to analyze the neural changes incident to the involution of the menopause. The resultant anemia and fibrosis of the genital tract must in some ways react upon the nearby nerves and nerve endings. Although estrogenic medication temporarily rejuvenates the tissues, it does not permanently arrest such involutionary diseases as leukoplakia (an epidermal process) or kraurosis (both epidermal and dermal). These processes appear to be irreversible.

Occasionally local rejuvenation by means of estrogens temporarily abolishes the itching of pruritus. This may be due in part to increase in the local circulation and return of the mucosa to a preclimacteric status. Possibly the relief may be due to a change of the vaginal secretion which in the menopause is alkaline (pH 7.5), premenopausally acid (pH 5.5).

From what has preceded, it is evident that hormonal and neural influences show many interactions. The evidence at hand is sufficient to convince that cortical and subcortical cerebral influences play a role. In the pelvis, however, endocrine action appears dominant, giving the vital genital sphere great independence but nevertheless not freeing it completely from nervous regulation.

I desire to thank Dr. Samuel R. M. Reynolds for much helpful advice, especially on the effect of the estrogens upon the autonomic nervous system of the pelvic organs.

SUMMARY

By gradual evolutionary processes, endocrine and neural interaction has become stabilized.

The focal point of this interaction appears located in the hypophysis—hypothalamus.

The estrogens affect the cerebral cortex to some degree though their mode of action upon the cortex is not understood.

The estrogens act directly upon the adenohypophysis which in turn may influence the hypothalamic nuclei. These nuclei, on the other hand, in response to nervous stimuli, can act upon the hypophysis.

The female generative organs are endowed with a large nerve supply, yet enjoy a far greater independence from nervous control than any of the other viscera. Their dominant control is hormonal.

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THE RÔLE OF ELONGATION AND CONTRACTION OF THE INFERIOR VENA CAVA, COINCIDENT WITH RESPIRATION, IN THE RETURN OF BLOOD TO THE HEART: REPORT OF AN OBSERVATION ON MAN

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In 1926 the author was present at an operation performed by Dr. W. Jason Mixter at the Massachusetts General Hospital, Boston, Massachusetts, in which the inferior vena cava had been exposed during left lumbar incision for lumbar sympathectomy. The patient (an adult male being operated upon for spastic paralysis of the left leg) was lying on the right side and breathing freely under ether anesthesia. Several inches of the inferior vena cava were completely exposed to view and showed remarkable elongation and shortening coincident with respiration. These changes were observed for some five minutes and the following points were noted:

With inspiration the inferior vena cava became shorter and thicker; with expiration it became longer and thinner. The variations in diameter amounted to approximately one-fourth to one-third. These variations were roughly estimated by Dr. Mixter by holding a pair of forceps parallel to the inferior vena cava.

The author was unable to find anyone among his colleagues who had made a similar observation and a preliminary survey of the literature failed to reveal observations of movements of the inferior vena cava in animals or in man.[1] In view of the fact, however, that the inferior vena cava is attached firmly to the diaphragm and to the base of the heart, as well as to the liver by means of the hepatic veins, and in view of the movement of the diaphragm and the liver with respiration, the upper or cardiac end of the inferior vena cava must rise along with the base of the heart in expiration and descend in inspiration. Consequently the inferior vena cava during inspiration would become bent or tortuous unless it contracted longitudinally, as observed. The reason why the movements of the inferior vena cava have not been observed more frequently may be ascribed to the fact that exposure of the inferior vena cava in man and in animals is ordinarily made through an abdominal incision, with the mesentery and liver held against the diaphragm in order to see the inferior vena cava. Thus, by pressure on the liver, the diaphragm is prevented from descending with inspiration and the movement of the inferior vena cava cannot occur. Subsequent examinations of a cat, a dog, a rabbit, a guinea pig and a monkey demonstrated that essentially the same phenomena occurred in these animals. In many of the lower mammals the renal veins are directed toward the diaphragm

[1] Leonard Hill, in Schäfer's Text Book of Physiology (loc. cit. 1) page 91, states: "The vena cava inferior passes through the central tendon of the diaphragm at a point which is immobile during the respiratory movements."

before joining the inferior vena cava and thus are also elongated and narrowed with the rise of the diaphragm.

The author has endeavored to evaluate the functional significance of these movements of the inferior vena cava, particularly with respect to the return of blood to the heart. His first impression was that an elastic tube, when elongated and narrowed by stretching, would decrease in volume. This, however, as suggested by Dr. J. H. Means, proved to be incorrect. Observations made both on a rubber tube of approximately the size of the human inferior vena cava and also on a specimen of human inferior vena cava, three to four hours post mortem, showed significant increase in volume on elongation and return to original volume on contraction.[2] Thus, on elongation, the influence of the decrease in diameter is more than compensated for by the increase in length. This confirms the observation of Braune (1) "Extension of the veins in their long diameter has been found to increase their capacity, and thus aspiration may be produced therein by alternate extension and flexion of the limbs."

It appears, therefore, that the inferior vena cava with expiration and ascent of the diaphragm becomes longer and narrower and increases in volume, thus accommodating and temporarily storing a larger amount of blood. This occurs when intra-thoracic pressure is increased and the flow of blood into the thorax thereby hindered. On inspiration, the reverse takes place; the inferior vena cava becomes shorter, thicker and decreases in volume, and the pressure within it is necessarily increased (abdominal pressure also increased). The additional blood previously accommodated in the inferior vena cava becomes forced into the right auricle just when intra-thoracic pressure becomes decreased, and the inflow of blood into the thorax is facilitated. Thus the inferior vena cava must act as a pump, working in synchronism with respiration, contributing to the return of blood to the heart.

Dr. Giles W. Thomas, who was working in the author's laboratory a few years later, made the important suggestion that the superior vena cava, being also firmly attached to the heart and practically continuous with the inferior vena cava at the right auricle, must also partake of the movement of the diaphragm. Thus with descent of the diaphragm in inspiration the superior vena cava would be elongated and increased in volume. The filling of the superior vena cava with blood during inspiration would be facilitated by the increasing negative intra-thoracic pressure (the superior vena cava lies wholly within the thorax and is exposed to intrathoracic pressure). In expiration the superior vena cava would shorten, diminish in volume, and force its additional blood into the right auricle, this action being aided by the increasing thoracic pressure of expiration. If these observations and deductions are correct, it would appear that the inferior and superior venae cavae act alternately as a beautifully coordinated double-action pump to aid in the return of the blood to the right heart, and that while such action is dependent primarily upon the movement of the diaphragm in respiration and upon the longitudinal elasticity of the venae cavae,

[2] The inferior vena cava is more abundantly supplied with elastic tissue than any other vein in the body. Many of the elastic fibers run longitudinally.

it is aided by the variations in intra-thoracic pressure as well as by the variations in abdominal pressure accompanying respiration.

With further consideration of the influence of the elongation and shortening of blood vessels upon their volume and upon the movement of blood within them, it becomes evident that many veins, especially those around joints and within muscles, are elongated or shortened by muscular movement (1).

The principle enunciated by Braune (1), that longitudinal extension of veins increases their diameter and that muscular movement by lengthening and shortening veins imparts to them a pumping action which facilitates venous blood flow to the heart, undoubtedly has application in the capillary and arterial circulation as well, and also in the lymphatic circulation. A more detailed discussion of the application of this principle will be the subject of another communication.

SUMMARY

Observation of the longitudinal extension and contraction of the inferior vena cava coincident with the rise and fall of the diaphragm in respiration is reported in man and in several lower animals. The volume changes in the inferior vena cava and in all probability in the superior vena cava coincident with respiration act as aids in the return of blood to the right heart. It is suggested that the volume changes coincident with elongation and shortening of blood vessels from muscular movement have a general significance in facilitating the circulation of blood throughout the vascular bed, as well as the circulation of lymph.

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ATYPICAL ACOUSTIC NEUROMAS[1]

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INTRODUCTION

Cases of tumor of the cerebello-pontine angle usually have a characteristic history and present a definitive clinical syndrome. The onset of illness is characterized by phenomena referable to the eighth nerve, both in its cochlear and vestibular divisions (tinnitus and vertigo). To these are later added nystagmus and corneal hypesthesia on the side of the lesion, thus completing the Oppenheim triad of symptoms. Frequently there is implication of the facial nerve. Pressure on the neighboring cerebellar pathways gives rise to homolateral cerebellar manifestations. The incidence of papilledema and increased intracranial pressure is due to interference with drainage of fluid from the cerebral ventricles by way of the Sylvian aqueduct. Later on, as the growth increases in size, there is dislocation of the brain stem to the opposite side. This may give rise to homolateral paresis with pyramidal tract signs.

At times, however, the patient has forgotten about the initial symptoms and the subsequent march of events. He comes to the physician in an advanced phase of his illness with the complaint of either rapidly advancing amblyopia or paresis of upper motor neurone type. It is in these cases that the examiner is put to it to unravel the complicated skein of circumstances and symptoms. Only by careful attention to the chronological development of the signs and symptoms can he hope to approach the solution of his problem. Aerographic studies are, of course, a great help but in one of our cases even this valuable aid in diagnosis failed at first to give us the proper clue. For these reasons we felt it worth while to report a group of cases of acoustic neuroma with bizarre clinical manifestations.

CASE REPORTS

Case 1. Sol R., a 37 year old salesman, was admitted to The Mount Sinai Hospital on October 26, 1926.

Chief complaints. 1) Headache and vomiting since May, 1925; 2) poor vision for one year, much worse for three weeks prior to admission; 3) uncertain gait for six months; and 4) drawing sensation in left wrist and left lower extremity for several weeks.

Family history. Irrelevant.

Previous history. Gonorrhea in 1914. Right-sided mastoidectomy in 1912. Recovery uneventful, but hearing had grown progressively worse on that side. Tinnitus and buzzing in both ears. No numbness in the face.

Present illness. In May, 1925, patient noted frontal headaches, especially in the morning. Vomiting came on at the same time and was described as "forceful."

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For one year prior to admission vision had been poor. During June and July, 1926 he saw double. Since then vision became so poor that he bumped into people and objects on either side of him; for three weeks prior to admission he could scarcely see with his left eye. For six months prior to admission, he could not walk well; had fear of falling when he walked rapidly or was going downstairs. For three months prior to admission his right hand seemed awkward. For five weeks prior to admission he experienced a drawing sensation in the left arm, wrist, hip and leg.

General examination. Eardrums perforated, retracted and scarred; a right mastoidectomy scar. Blood pressure 104 systolic and 75 diastolic. Chest and abdomen negative.

Neurological examination. Patient somewhat emotional and irritable. Head fixed and tilted, chin to left. Right upper extremity fixed in walking; gait ataxic, tendency to sway to the right. Succession movements impaired on right. Past-pointing with right hand. Speech not entirely clear. Deep reflexes: right more active than left. Plantars equivocal. Upper abdominals absent; lowers, left more active than right. Sensation intact.

Cranial nerves. High degree of papilledema with hemorrhages. Visual fields: tubular vision. Visual acuity: right 20/40, left 20/40. *No nystagmus*, but impaired conjugate movements of the eyes. Pupils: right larger than left; react well. Bilateral corneal hypesthesia. Right peripheral facial weakness. Loss of hearing in right ear, but bone conduction better than air conduction. Palate normal. Tongue deviated to left.

On the basis of mild hemiparesis with diminished abdominals and suggestive Parkinsonism on the right, absence of sensory changes, spontaneous past-pointing inward with the right hand, a lesion deep in the left temporal zone was postulated and exploration was advised. Subtemporal decompression on the right was carried out as a preliminary measure in order to save vision.

Patient became practically blind in the left eye and was able to count fingers only with difficulty on the right.

Encephalography was then carried out. The films showed symmetrical dilatation of the lateral ventricles; third ventricle not clearly seen; fourth ventricle and aqueduct normal; very little air on surface of the brain.

The encephalogram and the mild cerebellar signs suggested a lesion in the posterior fossa, but in view of the hemiparetic signs, exploration for left temporal tumor was performed. Ventricular puncture yielded 50 cc. of fluid. Incision was made into the left temporal lobe down to the ventricle. No tumor was found. No tumor cells were seen in tissue submitted to the neuropathologist.

Patient then spoke of further loss of hearing. Nothing local was found in the left ear to explain the deafness. Since this disturbance in hearing followed operation on the left temporal lobe (after previous right subtemporal decompression), the deafness was thought to be central in origin (bilateral temporal lobe injury).

Nerve deafness was later demonstrated on the right, but was thought to have been due to changes in the ear, secondary to an old infection. Caloric tests were not done due to perforations in the eardrums.

Post-neuritic atrophy later became manifest. Pyramidal tract signs on the right persisted. Gross hearing defects grew less, but the patient showed anomia, paraphasia, perseveration and jargon aphasia,—all indicative of a lesion of the left temporal lobe.

Laboratory data. Urine: negative. Blood count and smear: normal. Wassermann test of the blood: negative. Cerebrospinal fluid: clear; total protein 297 mg. per cent; 5 cells (lymphocytes); Wassermann negative; colloidal gold curve normal.

Patient was transferred to Montefiore Hospital on February 10, 1927, where he remained until October 9, 1928. The patient was disoriented, confused and showed what was described as mental infantilism. He received intensive deep x-ray therapy but his condition remained unchanged. He was then transferred to the New York City Cancer Institute with a diagnosis of probable subtentorial neoplasm. The neurologist at this institution thought he was dealing with a left frontal lobe tumor. The patient died on March 22, 1932. No autopsy was obtained.

Comment. In retrospect, one would have to say that we were probably dealing with an acoustic neuroma on the right. The right-sided deafness was misinterpreted; it was erroneously ascribed to the old ear condition (otitis and mastoiditis). The right-sided pyramidal tract signs were probably the result of *contre coup*. The encephalogram, which revealed a symmetrical internal hydrocephalus, makes this diagnosis most probable.

Case 2. Laura M., a 54 year old housewife, was admitted to Bellevue Hospital on September 21, 1931.

Chief complaints. 1) Weakness of the left arm and leg, 2) headaches, 3) impairment of hearing and tinnitus in the left ear.

Family history. Negative.

Previous history. Irrelevant.

Present illness. Weakness and awkwardness of the left arm and leg for four years. Headache for four years, chiefly frontal, progressively worse. Paresthesias of the left side of the face for possibly five years; at the time of admission these involved the lips, nose, left side of the face, tongue and gums. *Impairment of hearing and ringing in the left ear, for two years.* Pain about the left ear in recurring episodes. Facial weakness on the left, getting progressively worse. Weakness of the muscles of mastication. Dizziness, with true turning sensation. Double vision and bilateral blurring of vision for two years.

Neural findings included low grade papilledema with some secondary atrophy, coarse nystagmus, more pronounced to the left, diminution of the left corneal reflex, left lower facial weakness (chiefly mimetic), nerve deafness on the left (not complete), total absence of caloric responses on the left, left hemiparesis with spasticity, hyperactive tendon reflexes, ankle clonus and Babinski sign.

X-ray examination of the skull revealed increased vascularity, complete erosion of the posterior clinoid processes and irregularity of the floor of the sella.

Ventricular estimation showed the presence of internal hydrocephalus with free flow of fluid, suggesting a lesion of the posterior fossa. The ventricular fluid was clear and colorless. At the same time, further aspiration yielded xanthochromic and viscid fluid. (This was probably fluid from an accompanying cyst.)

Suboccipital craniotomy was performed. A tumor (acoustic neuroma) was found in the left cerebello-pontine angle; it was partially removed and the cyst above referred to was evacuated at the same time.

Comment. This was a case of angle tumor on the left with early jamming of the brain stem and right pyramid against the right side of the skull. The late development of deafness and its incomplete character seemed at first to exclude eighth nerve tumor. However, the absence of caloric responses spoke for it. Right cortical meningioma was also thought of on account of the left hemiparetic phenomena and increased vascularity of the skull shown in the x-ray films. The possibility of multiple metastatic lesions was also considered.

It seemed difficult to visualize a tumor in existence for many years, arising from the left eighth nerve and causing marked involvement of the opposite pyramidal tract without giving rise to profound evidence of increased intracranial pressure. The slow march of events probably made temporary compensation possible, although the increased intracranial pressure finally led to herniation downward to the floor of the third ventricle and the sellar changes described.

Case 3. Marion H., a 52 year old widow, formerly an actress, later a houseworker, born in Scotland, was admitted to Bellevue Hospital on June 21, 1933.

Chief complaint. Failing vision for three months prior to admission.

Previous history. Irrelevant.

Present illness. 1) Three years prior to admission patient treated a left earache with iodine and "lost hearing immediately." 2) Six months previously she experienced numbness of the left face. 3) Four months prior to admission she noted failing vision and diplopia with occasional "black spells"; vision became so poor that she had to stop work. 4) About one week prior to admission she noted slight ataxia and reeling gait. 5) Very recently, slight headache, frontal and occipital, made its appearance. No previous headache, vertigo, tinnitus or vomiting. She also spoke of some numbness of the face, arms and fingertips.

The general medical examination revealed the signs of a moderate hypertension (blood pressure 160 systolic and 120 diastolic) and slight enlargement of the heart to the left.

Neural status showed old bilateral papilledema with concentric contraction of the visual fields, fine nystagmus on lateral gaze, a little diminution in perception of pin-prick on the left side of the face, absence of corneal reflex on the left, slight left facial weakness with widening of the left palpebral fissure, diminution of hearing and impaired bone conduction on the left, slight dysmetria and tremor of the left arm and leg. Patient tended to fall to the left and backward, and showed some disturbance in succession movements on the left. There also were exaggeration of the deep reflexes, absent abdominals and suggestive Babinski on the left.

Barany tests were advised but unfortunately were not carried out.

The diagnosis of acoustic neuroma was made. Intracapsular removal of a left acoustic neuroma was carried out. Pathological diagnosis: perineurial fibroblastoma.

The patient later developed secondary optic atrophy and lost vision completely in the right eye.

She subsequently showed recurrent signs and it was thought that either fluid had reaccumulated in the angle or that there had been an actual recurrence, but she refused further operative interference. She died of pneumonia.

Comment. This patient presented as her chief complaint dimness of vision for three months and, for an even briefer period, slight ataxia on walking, numbness and tingling in the left face, but no vertigo or vomiting. It is to be stressed also that there was no tinnitus at any time and that the patient had forgotten about her loss of hearing three years previously.

Case 4. John L., a 45 year old furrier, was admitted to Bellevue Hospital on August 3, 1935.

Chief complaints: "pain in the left cheek bone just below the eye" and blurring of vision.

Family and previous history. Negative.

Present illness. 1) Neuralgic pain in the left side of the face since March, 1934. This pain persisted, with variations in intensity, from the onset up to the date of admission. There were no trigger zones in response to external stimulation. The pain was attributed by various physicians to an impacted wisdom tooth, sinusitis and other causes. 2) Five days prior to admission, progressive amblyopia with periods of transient "fog." In March, 1935 the right eye suddenly became "almost completely blind" and this condition persisted up to the date of admission. On admission, patient could read the paper with his left eye. Since then vision had been getting rapidly worse in the left eye as well. 3) Impairment of hearing in the left ear soon after the onset of original pain; no tinnitus at the onset. 4) Dizziness and tendency to fall to the left; no headache or vomiting.

Neural examination. Blurring of the optic discs with some pallor on the right. *No nystagmus.* Slight hypesthesia in the distribution of the left fifth nerve, including the cornea. No facial weakness. Diminished hearing on the left. History of slight tinnitus

within recent weeks but no vertigo. Other cranial nerves negative. No motor phenomena. No sensory disturbances on trunk or extremities. No cerebellar signs.

Visual fields. General contraction and enlarged blindspots.

Vestibular tests. Poor reactions from the horizontal and vertical canals on the left.

General medical examination revealed no abnormalities. Blood pressure 140 systolic and 110 diastolic.

Aspiration of the ventricles yielded 90 cc. of clear, colorless fluid. Ventriculography showed dilatation of both lateral ventricles but the third ventricle was not well visualized and seemed to be displaced upward.

In favor of the diagnosis of an angle tumor were the impaired labyrinthine reactions and the partial deafness; against it were the initial symptom of trigeminal pain, the absence of nystagmus or peripheral facial weakness and the failure to visualize the third ventricle. This led most of the staff to agree on a lesion of the left middle cranial fossa. On one examination, too, there was a suggestion of quadrantic defects in the visual fields. It was therefore decided to explore the left middle fossa. This was done, but no tumor was found.

The symmetrical internal hydrocephalus, however, was finally interpreted as indicative of a lesion in the posterior fossa and suboccipital exploration revealed a tumor of the left eighth nerve; intracapsular enucleation was carried out. Microscopic diagnosis was perineurial fibroblastoma.

Comment. The early appearance and prominence of the visual symptoms and the findings in the fundi were suggestive of a lesion near the chiasm. But the visual field defects were not consistently in harmony with this diagnosis. The signs referable to the fifth and eighth nerves suggested a lesion of the posterior fossa and this was supported by the impairment of caloric responses and the aerographic findings. The case was unusual in that the acoustic neuroma did not produce total deafness.

Case 5. Michael F., a 51 year old painter and laborer, was admitted to The Mount Sinai Hospital on October 19, 1935.

Previous history. Head trauma in 1913; not severe and no sequelae. Chronic alcoholism for years.

Present illness. 1) Generalized throbbing headache of four years' duration; 2) attacks of dizziness; 3) weakness in the right lower extremity with twitching in this limb and staggering to the right; these episodes were preceded by numbness in the right lower extremity and the patient fell on several occasions; 4) recurrent attacks of obscured vision for three years, coming on at irregular intervals, three or four times a day; 5) tinnitus and impaired hearing on the right for two years; 6) recent morning vomiting. Patient had worked, however, up to the time of admission.

General medical examination. Negative. Blood pressure, 136 systolic and 80 diastolic.

Neural status. Pupils irregular, unequal (left larger than right) and sluggish to light and accommodation; bilateral papilledema and enlargement of blindspots, exhaustible spontaneous nystagmus, coarser to the left, right lower facial weakness, diminished right corneal reflex, protrusion of tongue to the right, bilateral hearing defects of the nerve type, more pronounced on the right; right knee and ankle jerks greater than left; suggestive Babinski on right; abdominals diminished on the right. Sensorium clear.

Cerebrospinal fluid. Clear, colorless, pressure 180 mm. of water, total protein 145 mg. per cent, 1 cell, colloidal gold curve normal, Wassermann reaction negative. Blood Wassermann reaction, negative. Complete blood count, normal. Urine, negative. X-ray examination of skull, negative. (Calcified pineal in normal position.)

Encephalogram. No air in the ventricles; air present only in subarachnoid space and cisternae.

Auditory tests. Bilateral impairment of hearing of the nerve type; high tones not heard in the right ear.

Caloric tests. Right: diminished and delayed nystagmus. No past-pointing and no vertigo. Left: diminished and delayed nystagmus, but normal past-pointing.

It was the impression of the otologist that there was a severely damaged vestibular mechanism on the right. The patient had little vertigo from stimulation of any of the canals and the lesion was therefore localized in the posterior fossa.

Toward the end of his stay, the patient became more drowsy. Nystagmus to the right, which had only been suggestive, became more pronounced. Ventricular puncture was performed to relieve intracranial tension—80 cc. of fluid were obtained from the right ventricle. Patient died suddenly on November 2, 1935 from respiratory failure.

Clinical diagnosis was left frontal neoplasm.

Post-mortem examination revealed generalized arteriosclerosis. The brain showed flattened gyri and marked internal hydrocephalus. A cystic tumor was found in the right cerebello-pontine angle, extending to the internal auditory meatus on the right side of the pons and medulla. There was dislocation of the brain stem to the left. The fifth nerve was displaced and the seventh and eighth nerves were found in the mass.

Pathological diagnosis was neurinoma.

Comment. The low intrathecal pressure and the right-sided phenomena suggested a supratentorial lesion. The focal seizures in the right leg pointed to the left parasagittal zone (like Case 6). It was noted, however, that there were no personality changes or aphasia. The nystagmus, the impaired caloric responses and the marked internal hydrocephalus, demonstrated by aspiration of the ventricles, suggested the presence of a lesion in the posterior fossa.

Case 6. Patsy P., a 21 year old, single, plumber's helper, was admitted to Bellevue Hospital on May 17, 1938.

Chief complaints. Weakness and lack of coordination of the left arm and leg for two years prior to admission.

Previous history. At the age of ten the patient was struck by an auto and sustained lacerations of the scalp. There were no sequelae. He again sustained an injury of the scalp at the age of sixteen, but it was of a minor nature.

Present illness. 1) About two years before admission patient developed difficulty in balancing himself. This occurred especially when he was carrying heavy loads, and seemed to be due to "some trouble in the left leg." Symptoms gradually progressed until, at the time of admission, he had great difficulty in keeping his balance while walking; no numbness or pain in his legs. About one month prior to admission he noted a similar difficulty in the left hand; while doing his work as a plumber's helper he found he could not grip the handles of his tools with the left hand. 2) For one and a half years, difficulty in pronouncing words, something which he had not noted previously. 3) At times, difficulty in swallowing, especially fluids; occasionally had to wait before the swallowing reflex could be initiated. No bladder symptoms.

Patient was alert, cooperative, of normal intelligence; with good insight into his condition. He exhibited bouts of compulsive laughter which caused him embarrassment and which he seemed totally unable to prevent. These outbursts occurred most frequently when the right side of the body was pricked with a pin, when the reflexes were being elicited on the right, or when he was asked to look to the right.

On percussion of the skull there seemed to be tenderness in the occipital zone. No bruit was heard.

Neural status. Pupils equal and reacted well. Extraocular muscles normal except for a rhythmical horizontal nystagmus, more rapid to the left; bilateral papilledema; corneal reflexes diminished, especially the left. Slight weakness of the left lower face (central

type); pharyngeal reflex absent; impairment of hearing and poor bone conduction on the left but no lateralization of the Weber to either side. Other cranials negative. Speech thick. Visual acuity 16/20 in both eyes. Visual fields within normal limits.

Slight motor weakness on the left; no sensory disturbances; deep reflexes more active on the left; positive Babinski on the left; abdominals and cremasterics absent on the left. In finger-to-nose test on the left, definite cerebellar type of ataxia. Succession movements also impaired on the left. When the patient walked, the left arm did not swing as freely as the right.

Laboratory data. Urine, negative. Blood count, normal. Wassermann test of the blood, negative. Blood chemistry, normal. Lumbar puncture revealed slightly xanthochromic but clear cerebrospinal fluid; initial pressure, 360 mm. of water; total protein, 140 mg. per cent; colloidal gold curve, 0001211000; Wassermann reaction, negative.

A lesion of the right hemisphere with concomitant hydrocephalus was postulated. It was also suggested that there was some damage to the basal ganglia, cerebellar pathways and pons. The compulsive laughter was deemed a possible thalamic release phenomenon. The possibility of multiple lesions was also considered.

X-ray examination. Skull: no intracranial calcification; sella turcica large but clinoids well preserved; optic foramina normal. Chest: No infiltration of either lung.

Aerographic studies were carried out from above. Ventriculogram showed very little shift of the ventricular system. There was depression of the left lateral ventricle both anteriorly and posteriorly, widening of its side to side diameter and elongation of the right ventricle, all suggestive of a parasagittal lesion on the left.

Left fronto-parietal craniotomy was therefore carried out but no tumor was found. Following operation the patient had a series of generalized convulsions with cephalogyric and oculogyric crises to the right; he also showed a definite aphasia. It was later noted that the patient showed some personality changes and seemed depressed.

Following the original craniotomy, the patient slowly recovered his speech but the left facial paresis, the other left-sided signs and the uncontrollable laughter persisted. Cerebrospinal fluid pressure remained continuously high, and its protein content was 100 mg. per cent.

Vestibular tests and second ventriculography were advised for final diagnosis.

Otoscopic examination of ears showed retracted drums. Caloric tests revealed a somewhat hypoactive left labyrinth.

During August, 1938, the patient became increasingly drowsy. There was increasing deafness of the left ear. The left-sided pyramidal tract signs persisted.

A second ventriculogram was then performed. This time there was a more or less symmetrical internal hydrocephalus, indicative of a lesion in the posterior fossa.

The history was then carefully reviewed and the illness seemed to have begun with weakness in the left arm and leg and deafness of the left ear. In view of the horizontal nystagmus, the aerographic findings and cerebellar ataxia on the left, the diagnosis of neoplasm in the posterior fossa was more probable. Quadrigeminal plate tumor seemed excluded by the history and findings.

On December 28, 1938 a sub-occipital craniotomy was carried out. It revealed a vascular tumor under the left cerebellar hemisphere. The tumor was yellowish in color, fairly firm and had the typical appearance of an acoustic neuroma. Pathological diagnosis was neurofibroma. The patient developed pulmonary edema, respiratory collapse with subsequent bronchopneumonia and died.

Comment. This case presented left-sided pyramidal tract signs, cerebellar manifestations on the left and pseudobulbar phenomena, pointing to bilaterality of lesions. The early deafness had been forgotten. The first ventriculogram too was quite confusing. It was only later that the syndrome was clarified by functional ear tests and renewed aerographic studies.

Case 7. Max W., a 51 year old pedler, was admitted to Beth Israel Hospital on December 12, 1940.

Previous history. Negative, aside from a peritonsillar abscess three years previously.

Present illness. 1) Difficulty in vision of twelve months' duration. Patient had been near-sighted for many years, but for one year prior to admission there had been progressive diminution in visual acuity to a point where walking in the street was difficult and reading impossible. 2) Attacks of moderate frontal headache for two weeks. 3) Hearing in the left ear had been very poor for many years; for two months buzzing in that ear, but no vertigo. No numbness of the face or double vision.

General examination. Somewhat obese individual, a bit slow in his responses but quite cooperative. The positive findings included marked exophthalmos (probably due to myopia), elevated blood pressure (180 systolic and 118 diastolic), and a few external hemorrhoids.

Neural examination. Wide pupils which reacted sluggishly to light. Conjugate eye movements poorly performed in all directions, presumably because of pronounced exophthalmos. Fundi: myopic degenerative changes and bilateral papilledema. Visual fields: irregularly contracted (not typical). Visual acuity in both eyes: 2/200 without correction, 4/200 with correction. Defective hearing in the left ear. Other cranial nerves intact. Rest of neural status negative.

Laboratory data. Urine, normal. Blood count and blood chemistry figures, normal; Wassermann reaction, negative. Lumbar puncture findings: Initial pressure 270 mm. of water; fluid cloudy; total protein 270 mg. per cent; colloidal gold curve, normal; Wassermann reaction, negative.

X-ray examination of the skull: Marked enlargement of the sella turcica with destruction of the posterior clinoids and the dorsum sellae; numerous small osteolytic foci disseminated throughout the vault. The x-ray diagnosis was "multiple destructive osteolytic lesions of skull indicative of metastatic foci."

On the basis of the history and x-ray findings, the first clinical impression was that we were dealing with a peri-chiasmatic lesion; metastatic carcinoma, multiple myeloma and Schüller-Christian's disease were suggested as diagnostic possibilities.

Further x-ray studies revealed no involvement of other bones by any lesion which could be linked with the skull picture. Repeated urinalysis revealed no Bence-Jones protein. Metabolic studies showed a basal metabolic rate of minus 15, a normal fasting blood sugar, with a mildly diabetic tolerance curve; cholesterol, 192 mg. per cent with esters 78 mg. per cent. Calcium and phosphorus blood levels were normal (11.9 and 3.5 respectively). Phosphatase was 2.4 units. Serum protein values were normal. Bone marrow studies showed no evidence either of xanthomatosis or of multiple myeloma.

Since the X-ray Department felt that the skull lesion was metastatic, genito-urinary and gastro-intestinal studies were undertaken, but these as well as x-ray films of the chest revealed no neoplastic focus.

Study of the auditory and vestibular functions revealed nerve deafness and absence of vestibular responses on the left, suggestive evidence of an acoustic neuroma with secondary pressure effects on the sella, although the absence of involvement of other cranial nerves or nystagmus seemed to militate against this diagnosis.

Ventriculography was then performed. Ventriculogram showed a large symmetrical internal hydrocephalus including an enormous dilatation of the third ventricle.

On the basis of all the findings, it was agreed that the patient probably had a posterior fossa tumor, most likely in the cerebello-pontine angle. Sub-occipital craniotomy was undertaken. During this procedure the patient went into respiratory failure and was revived with some difficulty. The operation was abandoned. The next day the patient's general condition was good and since his vision had diminished to a point where he had only light perception, it was felt that craniotomy should not be further postponed; the patient was returned to the operating room about 48 hours after the first operation. Shortly after the dura was opened, however, his pulse suddenly failed, and soon thereafter his respiration

as well. All efforts at resuscitation were of no avail and the patient expired on the operating table. Partial autopsy permission was obtained. It revealed the presence of an acoustic neuroma on the left.

Pathological diagnosis. Meningeal fibroblastoma of the eighth nerve.

Comment. This patient entered the hospital with the complaint of advancing amblyopia and there were no cranial nerve phenomena aside from impaired hearing on the left. The x-ray films of the skull were confusing at first, but the subsequent evaluation of the disturbances referable to the eighth nerve, the sellar changes and the aerographic studies enabled the clinicians to make the correct diagnosis.

SUMMARY OF CASES

Case 1 presented as leading symptoms, amblyopia and paresis.

Case 2, like Cases 1, 5, and 6, also exhibited hemiparesis.

Case 3 presented chiefly failing vision. There were, in addition, however, suggestive signs of an angle lesion.

Case 4 exhibited left facial pain and blurring of vision.

Case 5 presented frontal lobe signs with mild angle phenomena.

Case 6 exhibited left cerebellar and pyramidal tract symptoms together with pseudobulbar laughter.

Case 7 showed increasing dimness of vision, old difficulty with hearing and concomitant high myopia.

DISCUSSION

The clinical data in the cases here reported confirm the observations of Cushing, Oppenheim and others. Very little has been added to this subject since Cushing (1) published his well known monograph in 1917 and since Oppenheim (4) called attention to the triad of symptoms characteristic of these cases. The only progress made in recent years concerned the nature of the lesion (now called perineurial fibroblastoma) and improvements in the operative approach to these growths.

Ordinarily, patients with acoustic neuroma are apt to seek help from the otologist. It is important therefore for him to evaluate with care the symptoms of patients who complain of tinnitus, advancing deafness and dizziness. In this connection, the writer would like to emphasize the importance of an accurate history of the march of events and the routine carrying out of functional ear tests in all cases with aural symptoms. Later on, when the angle syndrome is overlaid with neighboring and distant phenomena, the problem of diagnosis will challenge even the experienced clinician making use of all available diagnostic aids.

Errors in diagnosis arise when some of the classic signs are wanting or when some concomitant condition like that of a preceding disorder of the ear adds an element of confusion (Case 1). The clinical picture may also be obscured by the dominance of a particular symptom, such as trigeminal pain, facial spasm or paresis, and the contralateral hemiparesis of the body. Occasionally, a diag-

nosis of tumor is made when the lesion proves to be some other form of neural illness, such as a circumscribed collection of fluid in the lateral cistern from chronic inflammation of the meninges (2). In this connection it should be said that arachnoid cysts frequently overlie these growths and when they refill give rise to recurrence of symptoms. This was true of one of our cases. At times, local symptoms are so masked by the general pressure phenomena as to obscure the picture. This was observed in several of our cases.

One of the most frequent errors is to confuse tumors of the cerebello-pontine angle with tumors of the frontal lobe. This happened in four of our cases and Meyer (3) recently reported three instances of angle tumor simulating cerebral vascular disease. In such cases careful x-ray examination of the petrous bone demonstrating unmistakable dilatation of the internal auditory meatus, should prove very useful. In such instances, too, ventricular estimation and aerographic studies, with the demonstration of a large internal hydrocephalus, will help to place the lesion in the posterior fossa.

In one case reported by Weisenburg (6) the illness ran for a number of years under the guise of trigeminal neuralgia, similar to Case 4 of our series.

It is important to note that many observers, including the writer, have confirmed the original findings by Barany, who noted absence of reaction from the horizontal and vertical canals on the side of the lesion and diminished irritability of the vertical canals on the opposite side.

The first stage of the illness may be insidious and may last for ten years or more before pressure signs appear. The direction of growth seems to determine the type of symptom complex. Growth forward produces symptoms of pressure early, due to blocking of drainage from the ventricles; growth backward evokes pressure signs later but gives rise to cerebellar phenomena early.

Pressure on the pons and dislocation of the brain stem may lead to multiple cranial nerve palsies and vertical nystagmus. The loss of reaction from the vertical canals on the side opposite to the lesion is also ascribed to pressure on the pons and is explained by the more superficial location in the pons of the decussated fibers from the opposite vertical canals. Crossed hemiparesis and hemianesthesia may occur as a result of compression of the long ascending and descending tracts, as has already been indicated.

The nystagmus, when present, is usually coarse toward the side of the lesion and rapid toward the normal side. In the writer's experience, the incidence of true nystagmus is rare in supratentorial lesions and is presumptive evidence of disease in the posterior fossa.

CONCLUSIONS

Seven cases of atypical acoustic neuroma have been described. The importance of a careful history with the chronological march of events has been emphasized and the reasons for errors in diagnosis have been suggested.

I am indebted to Dr. I. S. Wechsler for the clinical data in cases 1 and 5, which were observed on the Neurological Service of The Mount Sinai Hospital.

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THE INHIBITORY EFFECT OF STEROID SEX HORMONES UPON THE GONADOTROPIC ACTIVITY OF THE HYPOPHYSIS

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The experimental studies of Smith and Engel (1927) Ascheim and Zondek (1927) and others have established the fact that the anterior hypophysis produces a substance, the gonadotropic hormone, which controls the growth, development and functional activity of the male and female gonads. In the female the gonadotropic factor is responsible for follicle maturation, ovulation, corpus luteum formation and estrogen and progesterone production. Subsequent investigations have revealed that somewhat similar gonadotropic substances are also produced by the placenta (chorionic gonadotropin) and by chorioepitheliomata and biologically related tumors. In women with normal pituitary and ovarian function gonadotropic hormone has been demonstrated in the blood and urine (Frank and Salmon, 1935).

Following the removal of both ovaries or their inactivation by x-ray or the natural menopause, large amounts of hypophyseal gonadotropic hormone appear in the blood (Fluhmann, 1929) and urine, (Zondek, 1931; Osterreicher, 1933; Lassen, 1934; and Frank, Salmon and Friedman, 1935). In a recent study it was shown that the hyperactivity of the pituitary can be demonstrated as early as four days after the removal of both ovaries in women (Walter, Geist and Salmon, 1940). This indicates a very delicate reciprocal relationship between the gonadotropic hormones of the hypophysis and the hormones produced by the ovary.

EFFECTS OF ESTROGENS UPON HYPERACTIVITY OF THE HYPOPHYSIS IN MENOPAUSAL WOMEN

When estrogens became available in sufficient amounts to be clinically effective in relieving menopausal symptoms, the question arose as to whether it was possible to suppress the abnormal production of hypophyseal gonadotropic hormone by the administration of estrogens. Such inhibition was demonstrated with estradiol benzoate (Frank and Salmon, 1935) and correlated with estrogenic effects in the vaginal mucosa (Salmon and Frank, 1936). Further studies have revealed that a similar inhibition of the hyperactive hypophysis could be effected with estriol glucuronate (Salmon and Frank, 1937) and stilbestrol (Salmon, Geist and Walter, 1940).

INHIBITORY EFFECT OF SUBCUTANEOUSLY IMPLANTED ESTROGENS UPON GONADOTROPIC HORMONE EXCRETION

With the demonstration that subcutaneous implantation of estrogen crystals is a therapeutic procedure of great practical merit (Salmon, Walter and Geist, 1939; Geist and Salmon, 1939; Salmon, Geist and Walter, 1940; and Salmon, Geist and Walter, 1941) the effect of the implanted estrogens upon the gonado-

tropic hormone production by the hypophysis was studied. The patients were implanted with either loose crystals or compressed pellets of α-estradiol or α-estradiol benzoate.

In thirty-seven cases gonadotropic assays were performed on twenty-four or forty-eight hour specimens for from six to nine consecutive days preceding the implantation. In twelve cases the assays were performed continuously on forty-eight hour specimens for periods varying from thirty-two to two hundred and seven days after the implantation; in twenty-five, gonadotropic determinations were done at intervals of seven to fourteen days. These studies have shown that implanted crystals are strikingly more effective than pellets (of comparable weight and identical chemical constitution) in inhibiting the hypophysis. Neither α-estradiol nor α-estradiol benzoate *pellets* were able continuously to inhibit the excessive excretion of gonadotropic hormone for longer than eight days. In contrast to this brief period of inhibition, patients who had been implanted with estradiol or estradiol benzoate *crystals* showed continuous inhibition for periods varying from fifty-seven to two hundred and eleven days.

INHIBITORY EFFECT OF ESTRADIOL ESTERS IN OIL UPON GONADOTROPIC HORMONE EXCRETION

A control series of ten patients was given a single injection of 25 mg. each of α-estradiol benzoate and eight were given 25 mg. of estradiol dipropionate, in solution in sesame oil. The effectiveness was measured by duration of symptomatic relief, as well as by the duration of estrogenic effects on the endometrium and vaginal mucosa, and by suppression of gonadotropic hormone excretion. Excretion of gonadotropic hormone was suppressed for periods varying from nine to eleven days. The brief duration of these suppressive effects of the estradiol esters in solution in oil stands in sharp contrast to the prolonged effects resulting from estradiol implantation.

INHIBITORY EFFECT OF ANDROGENS UPON THE HYPOPHYSIS

Effect of testosterone propionate upon gonadotropic hormone excretion in a female castrate. Following the demonstration that estrogens can suppress the secretion of gonadotropic hormone by the hypophysis, the question arose as to whether the male sex hormone (testosterone) exerted a similar effect on the hypophysis.

In 1937 Salmon reported suppression of gonadotropic hormone excretion in a human female castrate following treatment with testosterone propionate. The patient studied was forty-six years of age and had had an hysterectomy and bilateral salpingo-oophorectomy six years before. During a preliminary study of twenty days the urine was found to be constantly positive for gonadotropic hormone (the excretion varying from 13 to 27 R. U. per day). The patient was given 815 mg. testosterone propionate in solution in sesame oil in divided doses intramuscularly over a period of twenty-seven days. Individual doses varied from 10 to 50 mg. Gonadotropic assays were performed throughout the period of observation of ninety-two days. The gonadotropin began to disappear from the urine after 465 mg. of testosterone had been administered. For a period of

eighteen days the urine remained negative for gonadotropin; thereafter the hormone reappeared in the urine.

Effect of androgens upon gonadotropin excretion in the male castrate. In 1936 Frank and Salmon attempted to determine whether the newly available synthetic androgens, androsterone, dihydroandrosterone benzoate and testosterone influenced the gonadotropic hormone excretion in a male castrate. Because of the fact that only small amounts of the hormones were available at that time, the comparatively small doses used failed to demonstrate suppression of the gonadotropic hormone production. Subsequent studies (Salmon, unpublished) however, have revealed that gonadotropin production can be inhibited by the administration of large doses of androgens (testosterone proprionate) or estrogens (estradiol benzoate). Recently, Catchpole, Hamilton and Hubert (1942) have reported that gonadotropin excretion in men with primary testicular deficiency is markedly diminished following treatment with testosterone propionate.

Effect of progesterone upon gonadotropic hormone excretion. Following the demonstration of the effectiveness of the estrogens and androgens in inhibiting the gonadotropic activity of the hypophysis, the question quite naturally arose as to whether or not progesterone had a similar effect.

In earlier studies, attempts to demonstrate inhibition with amounts of the hormone which corresponded to what had been experimentally determined to be the physiologically effective dose, namely, 60 mg. was totally ineffective in diminishing the excretion of gonadotropic hormone. Three patients who were injected with larger amounts (70, 80 and 90 mg. respectively) also failed to show any appreciable decrease in the amount of gonadotropic hormone excretion.

Effect of pregneninolone upon gonadotropic hormone excretion. Inhoffen, Longemann and Serini (1938) synthesized a compound (Δ^4 pregnenin-20-on-3-ol-17; also known as pregneninolone, 17-ethinyl testosterone; anhydro-hydroxy-progesterone) which possesses an unusual variety of biological properties. This compound, which is chemically very closely related to testosterone and progesterone, has been shown to have: (a) a progesterone-like action (progestomimetic) in immature rabbits (Inhoffen and Hohlweg, 1938; and Ruzicka, Hoffman and Meldahl, 1938) being, furthermore, active when administered orally; (b) an estrogen-like action (estromimetic) on the uterus and vagina of adult and immature rats; (Salmon and Salmon, 1940) and (c) an androgen-like action (andromimetic) in chicks, (Emmens and Parkes, 1939; and Courrier and Jost, 1939) and capons, and that (d) it will maintain pregnancy in spayed rabbits (Emmens and Parkes, 1939).

In humans, pregneninolone has been shown to produce a progestational effect on the estrogen-primed endometrium (Salmon, Walter and Geist, 1939) and in large doses, has an estromimetic effect in estrogen deficient women (Salmon and Geist, 1940). Gonadotropic hormone studies were performed in three postmenopausal patients in order to determine whether this compound would inhibit the gonadotropic hormone excretion. These patients were given total doses of 30 mg. per day for two, four and six weeks respectively. During this time the excretion of gonadotropic hormone was not appreciably affected.

DISCUSSION

The ability to inhibit gonadotropic hormone production by the hypophysis is apparently shared by a number of the steroid sex hormones, namely, by the estrogens, estradiol and its esters, by estriol glucuronate, by stilbestrol as well as by the androgen, testosterone propionate. Progesterone and anhydrohydroxy progesterone do not appear to have this effect in the dosage that has been employed. The doses of progesterone used are admittedly much smaller than the doses of testosterone propionate, and it is conceivable, that if progesterone were administered in as large amounts (by weight) as testosterone, that the progesterone might demonstrate the same inhibiting effects upon the hypophysis. It is evident *that the most potent sterol sex hormone, as regards capacity to inhibit the hypophysis, is estradiol and its esters; and that the most effective means of achieving prolonged inhibition of the hypophysis is by administering estradiol compounds in the form of crystal subcutaneous implantation.* It is noteworthy, that the male sex hormone, testosterone, inhibits the female hypophysis and that, the female sex hormone, estradiol, has a similar effect on the male castrate hypophysis.

The inhibitory effect of the male sex hormone upon the female hypophysis has been demonstrated in women in a number of indirect ways, namely, by the fact that the male sex hormone can cause suppression of menstruation (Salmon, Walter and Geist, 1938, and Geist, Salmon and Gaines, 1938); inhibit ovulation (Geist, Gaines and Salmon, 1940); halt estrogen and progesterone production, (Salmon, Geist and Walter, 1939; and Geist, Salmon, Gaines and Walter, 1940); and produces involuntionary changes in the endometrium (Geist, Salmon and Gaines, 1938) and vagina (Salmon, Walter and Geist, 1938). These striking suppressive effects produced by the male sex hormone, which indicate a strong antigynecogenic action suggested the utilization of this property in the treatment of a number of female endocrine disorders in which the basic disturbance appeared to consist of an overactivity of the gynecogenic hormones, namely, functional menometrorrhagia (Geist, Salmon and Gaines, 1938; Salmon, Geist, Gaines and Walter, 1941) certain types of dysmenorrhea (Salmon, Geist and Walter, 1939) premenstrual tension (Salmon, Geist and Walter, 1939; and Salmon, 1941) and premenstrual mastopathies (Geist and Salmon, 1941).

Androgens have been used in the treatment of these disorders with very gratifying results. The high percentage of good therapeutic results obtained with androgens in these conditions has furnished support to the theory that, in the normal female, the female sex hormones (gynecogens) are balanced by the androgens; that when this balance is upset either as a result of overproduction of one or the other, or as a result of a deficiency of one or the other group of hormones, there results, in the event of a preponderance of the gynecogenic factors, menorrhagia, dysmenorrhea, or premenstrual tension; and in the event of a preponderance of the androgenic factors, oligomenorrhea, amenorrhea and hypertrichosis. The therapeutic effectiveness of androgens in dysmenorrhea functional menometrorrhagia and premenstrual tension could, according to this theory, be attributed to restoration of a normal estrogen-androgen equilibrium.

The studies reported here have demonstrated that both the androgens and estrogens can individually inhibit the normal as well as the hyperactive gonadotropic function of the hypophysis. Evidence is accumulating which indicates that androgens play an important physiologic role in the sex hormone metabolism of the normal woman. It appears from these studies that one of the functions of the androgens may be to act, in conjunction with the estrogens, as a physiolopic brake on the gonadotropic activity of the pituitary.

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AMAUROTIC FAMILY IDIOCY[1]

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INTRODUCTION AND A BRIEF HISTORICAL REVIEW

Amaurotic family idiocy is a term well chosen by its discoverer, with whose name that of Tay is often bracketed when this affliction is referred to as Tay-Sachs disease. It owes its uncontestable position as a disease entity to the early and fundamental observations of Dr. Bernard Sachs. It is, therefore, very appropriate that in a volume, issued in honor of a pioneer in American neurology, a prominent place be reserved for a review of the older and the more recent anatomical and clinical contributions to the subject of Amaurotic Family Idiocy, and for a consideration of views held on the pathogenesis of this heredo-degenerative affliction of the nervous system.

We need but go back fifty-five years, when Dr. Sachs was out of Medical School only five years, to find his first contribution on what he then considered arrested cerebral development. With this interpretation, and unaware of the somewhat earlier ophthalmologic observations by Tay (1), he (2) presented before the American Neurological Association and later published (1887) the anatomical changes in the brain of this disease which on clinical grounds, several years later, he named Amaurotic Family Idiocy.

It will please him, I am sure, but not at all surprise him, to note that this writer's views, expressed in a previous communication (3), almost half a century later, coincide with his original opinion that in this disease defective development is at work as the underlying, if not to say, the determining factor. Equally interesting is it to recall that his original description of the pathologic findings in the brain of his first case of this disease (2)[3] still forms the ground work of all that has been learned by many investigators during the subsequent fifty-five years. He observed the "great depth of all fissures and the comparative simplicity of these fissures; the great exposure of the island of Reil due to contractions and narrowness of surrounding convolutions; the bifurcation of the central fissure and its confluency with a broad and long Sylvian fissure." He, thus, drew attention to many stigmata of malformation or underdevelopment and found them to be paralleled by histologic evidence of arrested development. Here, too, his observations were accurate and as thorough as the staining methods available at that time would permit.[4] He recognized the ubiquity of the disease process in the cortical cells as disclosed by his statement, "In my search through-

[1] From the Laboratories, Neurological and Pediatric Services of The Mount Sinai Hospital, New York.

[2] Aided by a grant from Child Neurology Research (Friedsam Foundation).

[3] This paper is reprinted in full in this issue of the Journal of The Mount Sinai Hospital.

[4] Dr. Sachs recently brought to my attention the interesting detail that the preparation of the histologic material and the microscopic studies were carried out under the direct supervision of the great figure in American medicine, Dr. Van Gieson.

out the brain, I have not come across more than a half dozen, if as many, pyramidal cells of anything like normal appearance . . . the contours are rounded, and the cell substance exhibits every possible change of its protoplasmic substance." He regarded the disease process as primary, there being "no evidence whatever of a previous encephalitic process." He concluded that there was a "simple change affecting the cells and probably the white fibers." The question whether it was "mere arrest of development or arrest of development due to a previous inflammation," he answered by favoring the former.

For sometime he maintained the original view as to the probable pathogenesis of this disease (4), but as we allow the passage of another nine years we find that in 1896 (5) Sachs stressed the familial character of the disease having found the same affliction in the sister of his first patient. Two years later, in 1898, on studying additional material (6), he reached the conclusion that he was dealing with "a heredo-degenerative form of disease occurring in infancy and characterized by a triad of manifestations: an arrest of all mental processes; a progressive weakness of all muscles of the body, terminating in generalized paralysis; and by rapidly developing blindness, associated with changes in the macula lutea, the cherry red spot and optic atrophy."

At this time several new contributions were made on this subject by contemporaries of Sachs. Among them were those of Peterson and Hirsch. The former (7) describing a case under the then already accepted name "amaurotic family idiocy" confirmed the observations of Sachs and added his own to the effect that the disease changes were restricted to the cells of the cortex and medulla. He agreed that the condition was one caused by defective development.

Hirsch (8), in his report, called attention to Sachs' study of another case of amaurotic family idiocy in which the findings in the first case were corroborated, and mentioned three other cases, disclosing similar changes, which were studied by Kingdon and Russell (9). These, however, contrary to Sachs' concept of arrested development, were interpreted by them as an expression of a degenerative process of undetermined character. Hirsch emphasized the fact that the disease was more widespread then originally thought, for he found the characteristic changes also in the nerve cells of the gray matter of the spinal cord and, to a somewhat less pronounced degree, in the cerebellar cortex. Moreover, he noted degenerative alterations in the optic chiasm and optic tracts. He quoted Holden (10),[5] who informed him of finding similar changes in the retina of the same child. Thus, his main contribution, aside from describing the cellular changes in a somewhat greater detail as to form, size and condition of the nerve cells, was his disclosure of similar changes in other parts of the neuraxis. He, too, probably for lack of proper staining methods, found the glial apparatus uninvolved. Not without interest is the fact that when Hirsch and Sachs exchanged histologic preparations, they discovered an identity of the disease

[5] It is of more than passing interest that Holden already in 1898, had made use of Weigert's staining method with the result of being able to draw attention to the black granules which were later rediscovered by Schaffer.

process in their respective cases. Hirsch, rightfully, came to the conclusion that the disease was one affecting the entire nervous system, but was unwilling to accept the arrested development theory of Sachs. He clung to his belief that the disease was in the nature of an acquired toxic degeneration with the causative agent having been transmitted through the mother's milk. This view was not accepted by Sachs, since his first two cases of this disease were infants fed by wet-nurses.

Sachs continued to publish his observations on this remarkable disease[6] (11, 12), but from then on, with interest in this malady growing rapidly, cases reported by others began to appear in increasing numbers. Many of these dealt with typical instances of the so-called infantile form, but soon many atypical instances found their way into the literature, all of them enriching it with the results of comprehensive histologic studies.

Foremost among these contributors was Schaffer (13), who brought into sharp relief the original observations of Sachs, by focussing attention on the *swelling* of the neurons (cell body and dendrites), and on the ubiquity of the disease process, affecting not only the neurons, but also the glial apparatus. He maintained that since the disease was restricted to the "neuroectodermal derivatives" it could be regarded as a "selective, germ layer disease," and in that sense as a system disease. He further proposed the concept that the disease involved mainly the so-called *hyaloplasm* of the affected cells. This structureless cytoplasmic substance undergoes first a process of swelling, then passes through another change in which there is elaborated a coarse granular material that fills or replaces the cytoplasmic structure. He designated this material as *prelipoid* granules, which, as the disintegrating process advances, are converted into simpler fatty substances. The final alteration of the products of degeneration, according to Schaffer, takes place in the cell bodies of the glia, which act as macrophages, and, in the course of this process, are transformed into the so-called compound granular cells. He also thought that a cessation of myelination takes place as part of the disease process. Somewhat later, Sachs and Strauss (14) reported observations which, in part, confirmed the histopathologic findings of Schaffer. More recently newer observations on the modalities of the disease, particularly with regard to the involvement of the cerebellum and the white matter throughout the brain were recorded by several investigators, including Globus (15); further careful histologic studies were made by Hassin (16).

As the more recent clinical and anatomical studies of amaurotic family idiocy are approached, it is found that substantial knowledge is at hand: The disease is known to exist in several forms, and a clearer understanding is available on the relationship between the hereditary and familial afflictions of the nervous system.

FORMS OF THE DISEASE

As the foundation was being laid for a better understanding of the basic histologic character of the disease, somewhat too sharp a line of demarcation was

[6] See bibliography accompanying the Curriculum Vitae of Dr. Bernard Sachs.

being drawn between the several variants of amaurotic family idiocy. This situation was soon remedied as evidence accumulated leading to the conclusion that a common pathologic process underlies them all, there being only a difference in the intensity and in the extent of the pathologic process affecting the nervous system in the several forms of the disease. Nevertheless, it is still convenient to discuss the several accepted variants of the disease under separate subheadings, such as: *infantile, late infantile, juvenile and adult forms.* To this could be added still another subgroup, the *congenital form* which, of course, is of singular importance and for obvious reasons will be discussed together with the infantile form; and finally the form described in association with Niemann-Pick's disease.

THE INFANTILE (TAY-SACHS) FORM OF AMAUROTIC FAMILY IDIOCY

This is the best known variant of this disease. It has been studied most extensively, both clinically and anatomically, probably because it is the more prevalent type. As its designation indicates, it has its beginning in early infancy, usually at the end of the first six months of post-natal life. In some instances the first signs of the disease are noticed during the second and third months of life; and a case is reported by Epstein (17) in which the manifestations of the disease are said to have made their appearance during the second week of post-natal life. Still more recently a case was reported by Norman and Wood (18) in which the pathologic process was probably congenital. In the infantile form an apparently abrupt change in behavior of the afflicted child is first to draw attention as the previously lusty and active infant becomes listless. The infant still retains a healthy and well nourished appearance and often, as pointed out by Sachs (19), the child is unusually good looking. Progressive muscular weakness follows, so that within a brief period of time the child can no longer support the head and later can no longer make any muscular efforts. With this two other cardinal signs make their appearance: progressive loss of vision and advancing dulling of intellect. With the clinical picture fully unfolded, other features come to the fore—spasticity of the extremities, muscular twitchings, merging into massive clonic muscular movements. The latter are often precipitated by some external stimulation, such as the touching of the child, the manipulation of an extremity, and often by a loud sound. In a sense, the infant manifests features of decerebrate rigidity and the Magnus de Kleijn phenomenon has been elicited in some instances. The progressive loss of vision terminates in total blindness and a fundus examination reveals in the great majority of instances the cherry red spot in the macula. The absence of such a spot has been reported in some instances, but even there primary optic atrophy and some other changes in the macula are present. Hyperacusis, as already mentioned, is another quite commonly encountered phenomenon, capable of causing a generalized convulsive seizure. The terminal phase of the disease, which may take place within one or one and one-half years after the onset, finds the child in a state of extreme marasmus. The child no longer can take nourishment, is unable to swallow, and death occurs as the result of inanition.

CASE NO. P.M. NO. NAME AND SEX	FAMILY AND EARLY PERSONAL HISTORY	SYMPTOMS AT ONSET	SYMPTOMS AND SIGNS ON ADMISSION TO HOSPITAL	COURSE	SUMMARY OF ANATOMICAL FINDINGS	REMARKS
1 11135 J. S. F	Jewish; no consanguinity; no known familial disease; normal pregnancy, normal birth. Was not very strong, but otherwise seemed to make fair progress physically and appeared to do well mentally.	*At 8 months* could not hold up head or sit up. There was generalized muscular weakness.	*At 11 months* her eyes did not follow light. The pupils (previously dilated with homatropine) were fixed to light. The optic discs were pale, a cherry red spot was present in each macula. The liver edge and spleen were palpable.	The child remained in the hospital a little over one year, dying at the age of 2 years. She gradually became more spastic and during the last month passed through repeated generalized convulsive seizures during which the child would assume the position of carpo-pedal spasm (fig. 1).	A full description of pathologic changes affecting the nervous system is given in the text. The general post-mortem findings included; bronchopneumonia and atelectasis of lungs; small follicular cysts in ovaries; fatty changes in the liver. The liver, spleen, and lymph nodes were studied by the available adequate histologic methods and found to be free of lipoid material.*	Significant changes were found in the posterior lobe of the pituitary body, characterized by marked reduction in the cellular elements and by degenerative alterations in the remaining pituicytes, large granular bodies, probably inflated cell structures were observed. The typical alterations in nerve cells were found in the pancreas, Meissner's plexus, and in other abdominal viscera.
2 3865 H. M. F	Jewish; no consanguinity. Full term and normal delivery.	*At 5 months* began to manifest signs of retarded development, could not support her head and did not try to sit up. There was gradual decline in both her physical and mental state.	*At 18 months* the child was poorly nourished, the anterior fontanelle was open. The pupils reacted to light; the optic discs were somewhat pale; with indistinct markings. The maculae were large greyish white areas, each containing a large round red spot. There was weakness of the right extremities and involuntary movements were present in the tongue and lower lip. The liver edge and spleen were felt, each about 8 cm. below the costal margin.	The child took nourishment very poorly and died in advanced marasmus during the second day in the hospital.	For description of the pathologic changes affecting the nervous system see text. The post-mortem examination was limited to the head.	The enlargement of the liver and spleen and the appearance of the discs and the macular zone which is said to be more like that found in the Niemann-Pick variety of the disease (Rothstein and Welt, quoting Karelitz (20)) raises the question whether this case does not belong to the latter form.
3 3911 D. G. F	Jewish; no consanguinity; strong probability that two siblings died of same disease. The patient (full term and normal delivery) developed normally until 10½ months. Held up her head at 5 weeks and sat up at 4 months; shortly thereafter she began to regress.	*At 13 months* she appeared not to be able to see well; could no longer sit up or hold objects in her hands. *At 16 months* she developed twitchings of the mouth and face and jerky movements of her legs, easily provoked or accentuated by sudden noise.	*At 17 months* her pupils were dilated and fixed to light; she apparently was blind. The optic discs were white with cherry red spot in the maculae. There was nystagmus on lateral movements of the eyes. Slight touch would provoke rigidity of the extremities. The deep reflexes were hyperactive.	The child developed otitis media and died of terminal bronchopneumonia at the age of 25 months.	A full description of the pathologic changes in the nervous system is given in the text. The post-mortem examination was limited to the head.	

CASE NO. P. M. NO. NAME AND SEX	FAMILY AND EARLY PERSONAL HISTORY	SYMPTOMS AT ONSET	SYMPTOMS AND SIGNS ON ADMISSION TO HOSPITAL	COURSE	SUMMARY OF ANATOMICAL FINDINGS	REMARKS
4 4148 M. B. F	Jewish; no consanguinity; one sibling developed signs of amaurotic family idiocy at 11 months and died at 3 years. Another sibling is living and well. The patient developed normally for the first six months.	*At 6 months* she could not hold up head or sit up. Developed spasmotic movements of arms and legs. *At 8 months* she was blind and could not distinguish voices. The fundi disclosed the typical findings in the disease and were recognized as such by the family physician.	*At 14 months* the child was blind, but the pupils reacted to light. The cherry red spot was present in each macula. The legs were spastic, R > L, and the deep reflexes were exaggerated. Hyperacusis was present. The fontanelles were 3 fingers open; only four teeth were present.	The child died shortly after entering the hospital of bronchopneumonia.	A full post-mortem examination disclosed the following: Diffuse fat infiltration of the liver; hyperplasia of pulp cells in the spleen; normal adrenals. The alterations in the brain were typical of the infantile form and were more like those seen in Case 1.	The posterior lobe of the pituitary body exhibited changes similar to those noted in Case 1, as could be detected by routine staining methods; no material was available for Schaffer's method.
5 4178 R. S. M	Jewish. Parents were second cousins; 1 sibling with retarded development, died of pneumonia. The patient was a full term, normal delivery. Early development appeared to be normal during the first three months.	*At 4 months* became listless, would not follow objects and would stiffen in response to sudden noise. The abdomen became distended and obstipation developed. Had pneumonia one month before entering the hospital.	*At 18 months* the child appeared acutely ill. She lay in a state of opisthotonus and exhibited carpo-pedal spasms. The pupils did not react to light; the discs displayed primary optic atrophy and a cherry spot in each macula. The extremities were rigid. The deep reflexes were hyperactive.	She developed a purulent otitis media. At the end of one week a positive blood culture was obtained for streptococcus hemolyticus. The child declined progressively and died at the end of the seventh week in the hospital.	Post-mortem examination was limited to the skull and its contents. The findings in the nervous system were similar to those noted in Case 1.	
6 4180 S. W. F	Jewish. Normal delivery and normal early development.	*At 3 months* began to take feedings poorly, drooled saliva, displayed twitching of the eyelids. *At 6 months* would stiffen at slight noice. *At 11 months* she appeared to be blind, and began to waste. At no time could she hold up her head or sit up.	*At 11 months* the pupils reacted sluggishly to light; the discs were atrophic and the cherry red spot was found in each macula. All the extremities were spastic and the deep reflexes were hyperactive. The child would startle at slight noise (hyperacusis). Carpo-pedal spasms would occur continually during which a posture of opisthotonus was assumed. The liver edge	The child developed erysipelas and died two months after admission.	Post-mortem examination was limited to the skull and its contents. The changes in the nervous system were typical and showed no unusual deviations.	

7 5118 B. K. F	Jewish. Normal birth and delivery. Father began to walk at 4 years. One sibling died of amaurotic family idiocy at the age of 2 years. The patient supported her head at 3 months and sat up at 6 months.	*At 7 months* she could not hold up her head or sit up. Could not swallow solid food. Showed both mental and physical deterioration.	*At 15 months* pupils did not react to light; optic discs were pale, a cherry red spot was present in each macula. The deep reflexes were depressed. The child would often manifest generalized spasticity with the lower extremities becoming extended and inverted, while the upper extremities would stiffen. Hyperacusis was present.	The child died of bronchopneumonia 12 days after admission to the hospital.	Full post-mortem examination revealed: acute confluent bronchopneumonia; a liver normal in size, shape and position; normal spleen. The adrenals were also negative. Special stain disclosed no lipoid storage in the liver, spleen or lymph nodes. The alterations in the nervous system were typical of the infantile form of the disease.	
8 5789 S. K. F	Jewish. Normal birth and delivery. Two siblings died of "familial idiocy." One paternal aunt had children with similar affliction.	The onset of the fatal illness was undetermined; the child was never able to hold up head or sit up; she never followed objects. *At 4 months* she lay listless in bed. *At 10 months* she would be startled by sudden noise. *At 14 months* she had repeated convulsive seizures.	*At 14 months* the child was listless, cried only occasionally and feebly. The pupils reacted sluggishly to light. A cherry red spot was present in each macula. The muscles were weak; the deep reflexes hyperactive; the abdominal reflexes were absent. There was a bilateral Babinski sign. Hyperacusis was present. Hydrocephalus was demonstrated by pneumoencephalography. The child was subject to repeated generalized convulsive seizures.	The child died of bronchopneumonia at the age of 15 months.	Post-mortem examination was limited to the skull and its contents. The histologic findings in the central nervous system were typical. The Purkinje cells in this instance showed the spongy appearance of the cytoplasm (fig. 32).	The posterior lobe of the pituitary showed marked disintegration of cellular elements, there being present only a few pituicytes.
9 6354 N. S. F	Jewish. No consanguinity. Normal delivery.	Age at onset uncertain. Mother did not suspect anything until the child was 13 months old, when she was told by physician who treated the child for a mild infection that it had amaurotic family idiocy. At that time the child could not sit up, follow objects, or recognize parents.	*At 18 months* the child was listless, would respond only to sudden noise. Eyes were in constant motion. A cherry red spot was present in each macula. The upper extremities were rigid, held in internal rotation with the fist half clinched.	A splenic biopsy was done. The child died shortly thereafter at the age of 18 months.	Full post-mortem examination revealed: acute fibrinous purulent pleuritis; acute fibrinous pericarditis; atelectasis of left lung; parenchymatous degeneration of the liver, kidneys and spleen. Storage of lipoid material was searched for by special methods and was not disclosed.	The posterior lobe of the pituitary revealed most advanced changes, containing a large number of globoid granular bodies (fig. 33).

TABLE 1—*Concluded*

CASE NO. P. M. NO. NAME AND SEX	FAMILY AND EARLY PERSONAL HISTORY	SYMPTOMS AT ONSET	SYMPTOMS AND SIGNS ON ADMISSION TO HOSPITAL	COURSE	SUMMARY OF ANATOMICAL FINDINGS	REMARKS
10 9974 U. L. F	No significant family history. Normal birth.	*At 6 months* the child became listless, would not sit up or follow objects. There was explosive laughter in paroxysms, lasting 20 minutes. Extensor spasm and grimacing was continuous.	*At 15 months* the child was well developed physically. The pupils did not react to light. The discs were pale, R > L. A cherry red spot was present in each macula. The muscles were flaccid, but the deep reflexes were hyperactive. There was hyperacusis.	The child developed an otitis media, followed by bronchopneumonia, terminating in death at the age of 18 months.	Full post-mortem examination disclosed: acute infectious splenic softening; fatty changes in the liver; a patent foramen ovale and bronchopneumonia. No storage of lipoid material was disclosed in the liver, spleen and lymph nodes by adequate staining methods. The adrenals were normal, but at the periphery disclosed a ganglion with cells displaying the typical alterations (fig. 34).	Only a small part of the posterior lobe of the pituitary was available. It showed quite advanced cellular disintegration. In the brain the cell changes were typical, except for good preservation of nuclei in some cell groups (fig. 35).
11 12150 K. Z. F	Late infantile? The mother had one miscarriage. Father suffered from Buerger's disease. The child was developing well until 1 year of age.	*At 12 months* regression was noted in behavior. She no longer would follow objects, lost acquired speech and developed convulsive seizures; could no longer sit up or hold up her head.	*At 18 months* the pupils reacted sluggishly to light. The optic discs were pale, the cherry red spot was present in each macula. There was some weakness of the *recti externi*. Tonic spasm would repeatedly affect the upper extremities and was accompanied by tremor of the hands and rolling of the eyes.	The child developed bronchopneumonia and died on the sixth day in the hospital.	Full post-mortem examination revealed: Patchy hemorrhagic bronchopneumonia; patent foramen ovale. The liver, spleen and lymph nodes were studied by special staining methods and revealed no unusual lipoid storage. The extrinsic nerve cells showed typical changes.	The posterior lobe of the hypophysis was very poor in pituicytes.

* The special search for lipoid storage in the various viscera in this as in the other cases of this group were made by Dr. Klemperer, to whom I am indebted for these findings as well as for the report on the general post-mortem findings.

ILLUSTRATIVE CASES

In the course of the past twenty years, a relatively large number of cases of the infantile form of amaurotic family idiocy have come under clinical observation at The Mount Sinai Hospital. Of these a large quota became available for anatomic studies (Table I). Several of them were selected for a more detailed presentation of their histologic features because they exhibit some striking deviations alongside the typical clinical and anatomical manifestations of the disease.

Case 1. Anatomical observations. Gross: The leptomeninges contain an increased amount of somewhat opaque cerebrospinal fluid. The brain is pale and firm to touch, giving it a rubbery feel. The gyri are small and are separated by wide sulci. The optic nerves are thin and very white, while the optic chiasm is ribbon-like flat. The cerebellum appears unusually small. Internal hydrocephalus is disclosed on sectioning of the brain.

Microscopic: The *leptomeninges* are somewhat thickened and exhibit a wide subarachnoid space which contains a large number of large round cells in the character of compound

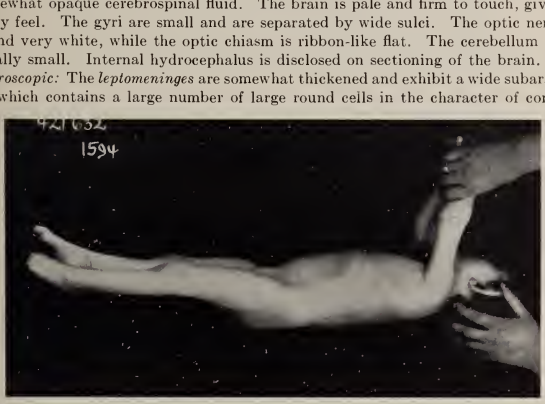

FIG. 1. Photograph of the infant (Case 1) during a convulsive seizure, exhibiting carpopedal spasm.

granular cells. There are no inflammatory alterations, such as diffuse or perivascular lymphocytic infiltration.

Cerebral cortex: Nissl preparations under low magnification disclose a diffuse disturbance in the cytoarchitecture of the gray matter (fig. 2). The lamillar arrangement is no longer well defined. This is due to several factors, the most important of which are the loss of nerve cells, the unusual increase in size of the remaining nerve cells and, finally, the increase in number of glial elements with particular emphasis on the compound granular cells. These alterations are found throughout the cerebral cortex, without any striking predilection for any special cortical layer or zone.

The individual cell changes in their outspoken character are those typical of the disease. The cell has lost its angular or pyramidal shape; it has acquired a plump, ballooned-up, rounded or ovoid outline (fig. 3). The nucleus is displaced to the periphery or to the axonal base; it is often shrunken, pyknotic or altogether missing. The tigroid substance has disappeared, leaving in its place the pale, slightly granular or spongy cytoplasm. Only an occasional cell shows an inflation of a dendrite or axon (much more prevalent in Case 2), and very few are the cells which have retained a somewhat pyramidal outline. Such cells show very little, if any, tigroid substance, while the residual cytoplasm is vacuolated or coarsely granular. In between the nerve cells there are encountered many swollen, rounded glial elements which bear a strong resemblance to compound granular cells.

Silver preparations stained by the Bielschowsky method disclose many features as to size, form and cytoplasmic contents which to a great extent conform with those noted in Nissl preparations. But in addition they disclose alterations in the endocellular fibrillae. The latter are displaced to the periphery where they form fairly thick bands (fig. 4). It is significant that these fibers, constituting the conducting apparatus of the nerve cells, are relatively well preserved although displaced and probably distorted. The center of the cell thus freed of fibrillae is occupied by coarse granules and debris-like material, or is often almost completely devoid of visible material.

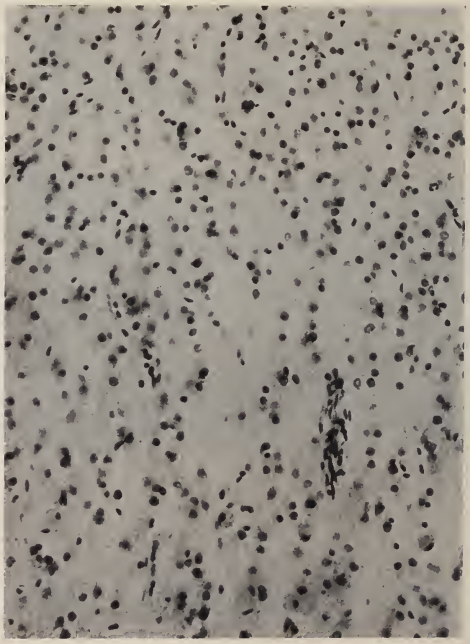

FIG. 2. Section of the cerebral cortex (Case 1), showing the marked disturbance in its cytoarchitecture due to cell loss, resulting in focal areas of rarefaction; to the swelling of individual nerve cells; and to the increase of glial elements. Nissl stain, × 225.

Sections stained by the method of Schaffer, a modification of the Weigert-Kulschitsky stain for myelin, offer a remarkable display of cell alterations. The nerve cells as well as the accompanying rounded glial elements are crowded with numerous well formed spherical granules, dark blue in color (fig. 5). In the midst of the granules there is visible the nucleus of the nerve cells, but the greater density of the granules in the glia cells obscures the nucleus in the latter.

A similar, almost specific staining reaction is obtained by the gold sublimate method (the Globus modification of Cajal). Here the so-called prelipoid granules in both the

nerve cells and the rounded glia cells appear as bright red, somewhat darker in the glia (fig. 6).

Preparations stained by the Herxheimer, scarlet red, method for the demonstration of neutral fats exhibit numerous fine, light rose colored granules in the cytoplasm of the nerve cells and coarse, bright red granules (fig. 7) in the glial elements, rounded or branching.

Cerebellar cortex: There is a fairly uniform reduction in the width of the folia with a corresponding reduction in the number of cells in the granular layer. The Purkinje cells are also reduced in number and thus display a great irregularity in their distribution and alignment (fig. 8). The remaining Purkinje cells show striking alterations, disclosing advanced stages of disintegration. The cell bodies are unusually large. Their processes are markedly inflated. There is not a vestige of tigroid substance in the cytoplasm and endocellular fibrillae are reduced in number, displaced, distorted, or altogether missing. The cell bodies are filled primarily with granular or amorphous material. Their dendritic

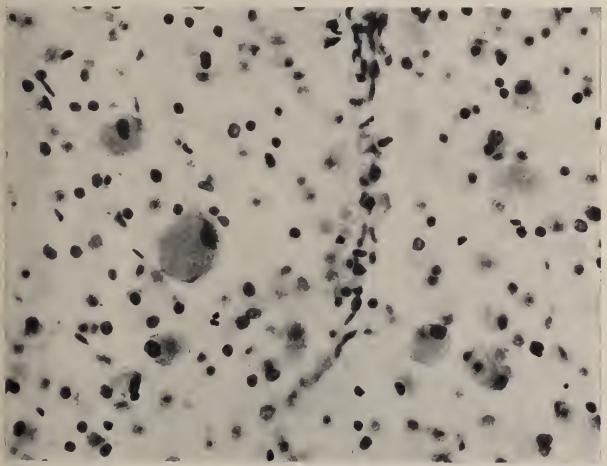

FIG. 3. Swollen, rounded, and otherwise altered nerve cells (shown in fig. 1) under higher magnification. Nissl stain, × 400.

processes are filled with similar material. Here little is left of the conducting apparatus (fig. 9). Only a few fibrillae are visible at the periphery of the process, which consists mainly of yellow granular debris. In sections stained by the Schaffer method the prelipoid granules are less crowded and take on a much lighter stain (fig. 10). This as well as their rather poor staining reaction in all probability indicates that the loss of the prelipoid material is part of the disintegrating regressive cell process. Fat stains reveal features very much like those seen in the cerebral gray matter.

Brain stem: The nerve cells in the basal ganglia, midbrain, pons and medulla oblongata display changes similar in character to those seen in the cerebral and cerebellar cortex. Here, however, (as shown in the cells of the oculo-motor nucleus (fig. 11 A, B)) some tigroid substance has been retained in the perinuclear zone. Sections stained for myelin exhibit little, if any, loss of myelin of the projectile tracts (fig. 12).

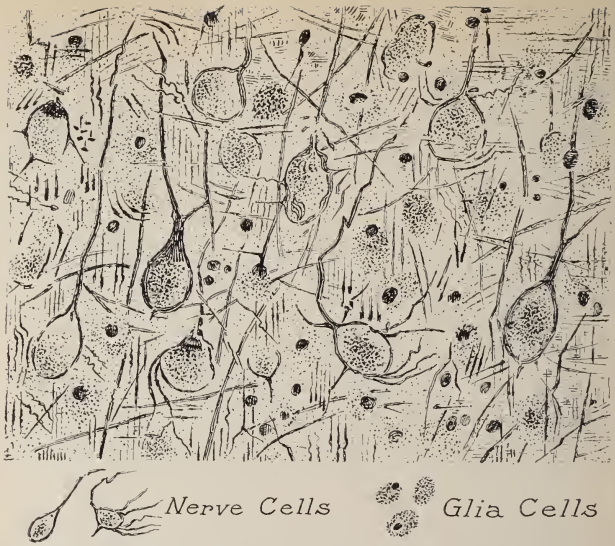

FIG. 4. Drawing, illustrating the nerve cell changes in the cerebral cortex (Case 1) as seen in a silver stained (Bielschowsky) preparation.

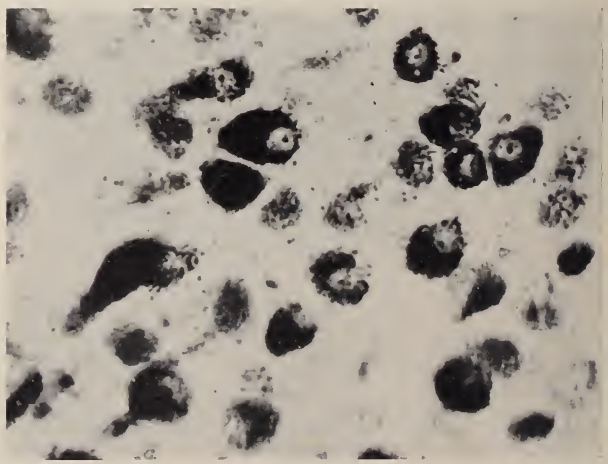

FIG. 5. Nerve cells (larger) and glial elements (smaller and less densely stained units) filled with prelipoid granules, in the cerebral cortex (Case 1). Schaffer's modification of Weigert's myelin stain, × 635.

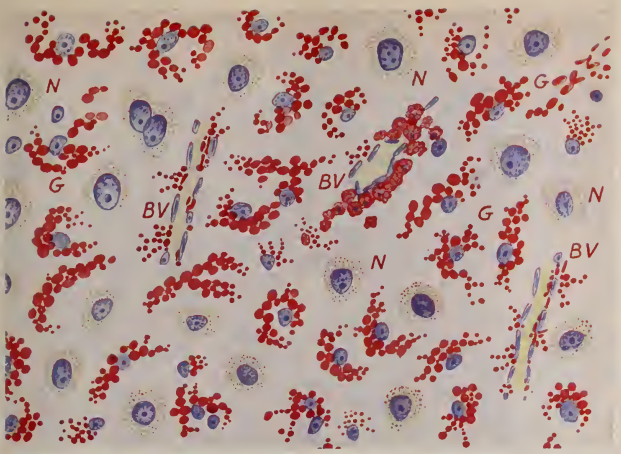

FIG. 6. Drawing of the cerebral cortex (Case 1) showing nerve cells (N), glial elements (G), and blood vessels (B.V.), displaying free fat, varying in amounts and in the size of the granules. Herxheimer's scarlet red stain.

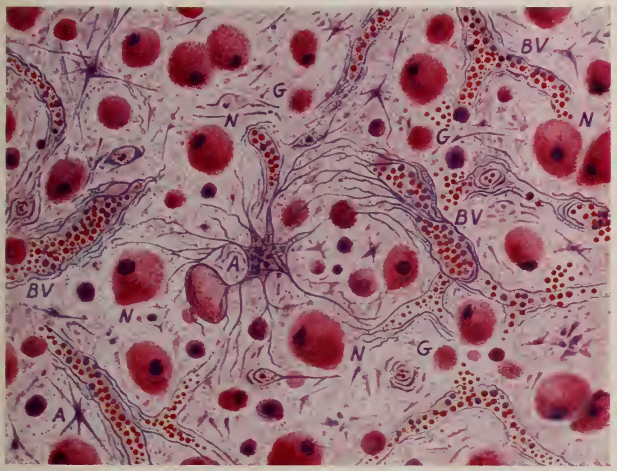

FIG. 7. Drawing of the cerebral cortex (Case 1), showing the staining reactions of the prelipoid granules in the nerve cells (N), and the glia elements (G). Note also the large fibroblastic glia stained black. Cajal's gold sublimate stain (Globus modification).

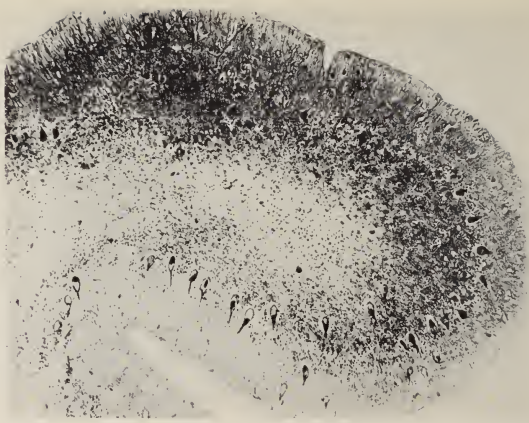

FIG. 8. Section of the cerebellar cortex (Case 1) exhibiting irregularity in the alignment of the Purkinje cells and the irregular reduction of their number. Bielschowsky silver stain, × 50.

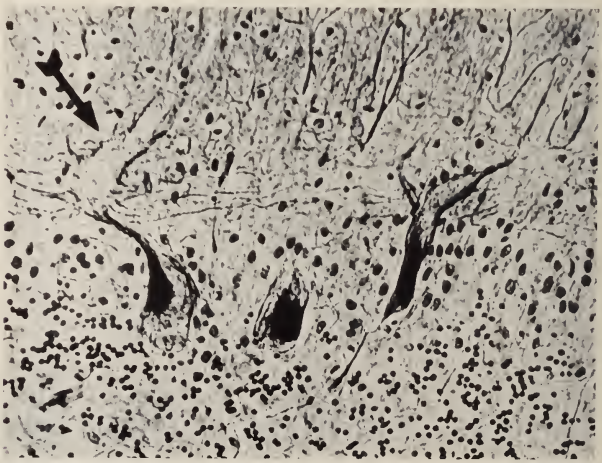

FIG. 9. Purkinje cells (exhibited in fig. 8) under higher magnification. They display, in addition to the characteristic cell body alterations, marked inflation of the dendrites. The arrow points to the argentophylic fibrillae which were displaced to the periphery thus revealing the limits of the inflated portion of the process. Bielschowsky silver stain, × 300.

Subcortex of the cerebrum: The more significant alterations here are characterized by a diffuse, quite uniform mobilization of fat-laden compound granular cells as disclosed by the scarlet red staining method (fig. 13 A). The fat containing cells are arranged in parallel lines, suggesting a recent demyelinating process affecting the fibrous tracts (fig. 13 B). Diffuse gliosis in the subcortex is well shown in preparations stained by the gold sublimate staining methods (fig. 14). Myelin stained sections, however, show only a mild loss of myelin in any part of the subcortex.

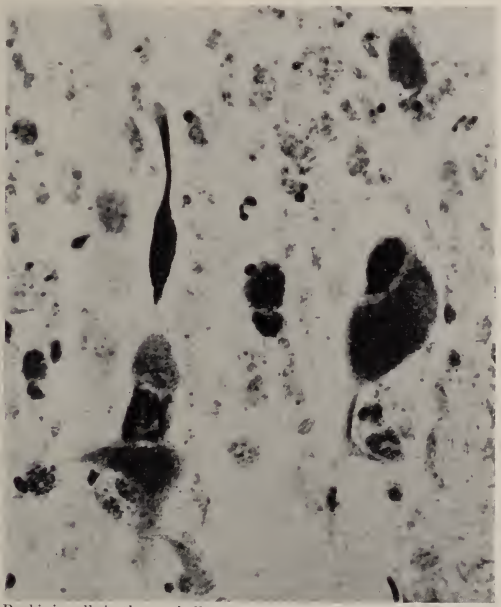

FIG. 10. Purkinje cells in the cerebellar cortex (Case 1), exhibiting the prelipoid granules in the cell body and its processes. Schaffer's modification of Weigert's myelin stain, × 525.

Subcortex of the cerebellum: The white substance alterations here are similar to those noted in the cerebral cortex.

Spinal cord: The cell changes similar to those noted elsewhere in the nervous system are found here affecting cells in all columns; motor, sensory, visceral and association groups. The white matter shows very little change in the character of demyelination. The long ascending and descending tracts are well preserved.

Extrinsic nerve cells: A thorough search for changes in nerve cells outside of the brain and spinal cord is rewarded by highly instructive findings. Nerve cells in the submucous plexus of *Meissner* (fig. 15) show changes similar to those found in the nerve cells of the brain and spinal cord. The same is true of nerve cells found in a small ganglion in the pancreas (fig. 16 A). A cell exhibiting the same alterations is found in the wall of the

urinary bladder (fig. 16 B). A group of cells showing similar changes is present in the periphery of the adrenal. The medulla of the adrenal which is neuroectodermal in derivation shows no pathologic changes.

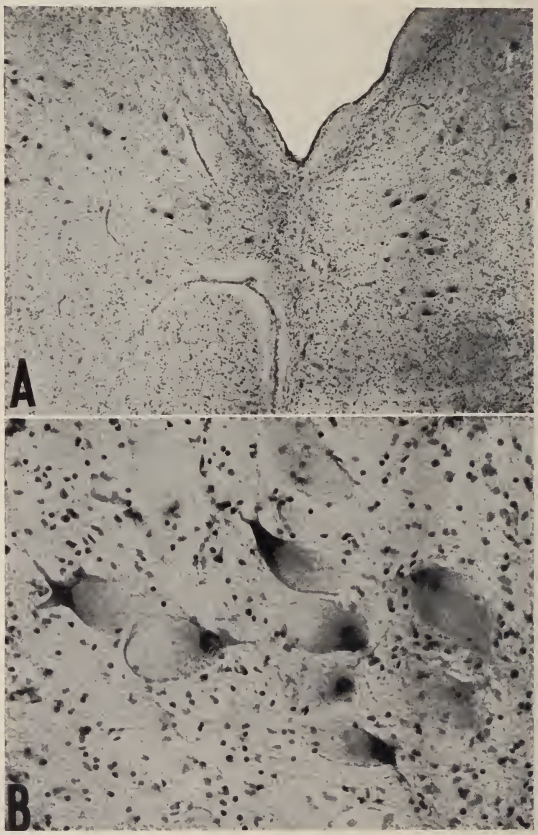

FIG. 11. Nerve cell alterations in the nucleus of the oculomotor nerve revealing better preserved cell nuclei and paranuclear remnants of tigroid substance. Nissl stain, A × 53; B: × 275.

The pituitary body, in its posterior lobe, is the seat of alterations which, though readily understood, are striking since to my knowledge they have not been previously reported

The pituicytes are greatly reduced in number as shown by the rarefied cellular appearance of this structure. They show also disintegrating changes such as swelling and distortion of outline (fig. 17). Among them there are many large globoid bodies filled with granular material. Occasionally these bodies contain a central deeply stained rounded body simulating a pyknotic nucleus (fig. 18). The impression is gained that this is a nerve (ganglion) cell undergoing alterations typical of the disease.

Summary: A child who, at the age of eight months, began to display evidence of mental and muscular regression, died at the age of two years of what was definitely diagnosed as amaurotic family idiocy. The anatomic investigation revealed the typical cell changes: swelling of the cytoplasm, elaboration of a granular prelipoid substance in the cytoplasm, inflammation of dendritic processes of the Purkinje cells, and only occasionally of cells in the cerebral cortex or brain stem. The prelipoid cell content reacts variously with the several

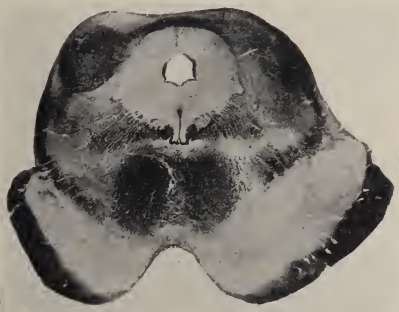

FIG. 12. Cross section of the midbrain (Case 1). Weil's myelin stain, × 4

staining methods. With scarlet red and osmic acid (Marchi), the nerve cells show only a slight coloring. This coloring is more intense with the Schaffer stain and with the gold sublimate method. In the glia cells, on the other hand, the prelipoid substance stains a deep red with scarlet red and a bluish black or purplish color with the gold sublimate method. Compound granular cells are quite prominent in the gray substance and particularly in the white substance. The fibrous glia are present to some extent in the white, but are more numerous in the rarefied zones of the central cortex. To all this may be added the marked degeneration of the axis cylinders and demyelination, and the somewhat greater involvement of certain cortical layers. Of significance also is the finding of typical alterations in the nerve cells distributed through some abdominal and pelvic viscera (intestinal tract, pancreas, adrenals and urinary bladder). No less significant are similar alterations in the pituicytes with formation of large intercellular granular (colloid) bodies.

FIG. 13. A. Section of the frontal lobe, showing accumulation of neutral fat, most marked in the subcortex. Herxheimer's scarlet red stain, × 90. B. A field in the subcortex (shown in fig. 13A), exhibiting under higher magnification the alignment of the fat globules. Herxheimer's scarlet red stain, × 290.

The general post-mortem findings are of significance only so far as they exclude the presence of alterations in the liver, spleen and lymph nodes, such as are characteristic of Niemann-Pick disease.

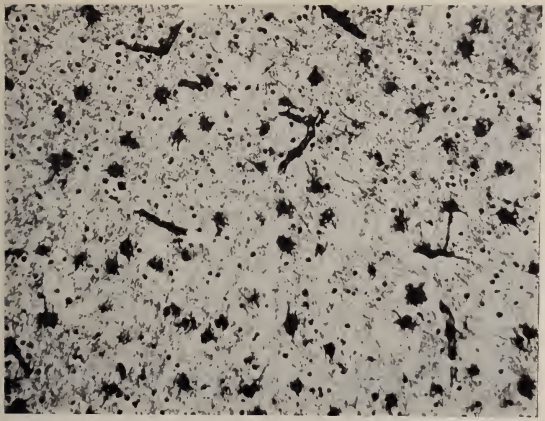

FIG. 14. Gliosis of the cerebral subcortex (Case 1). Globus' modification of Cajal's gold sublimate stain, × 190.

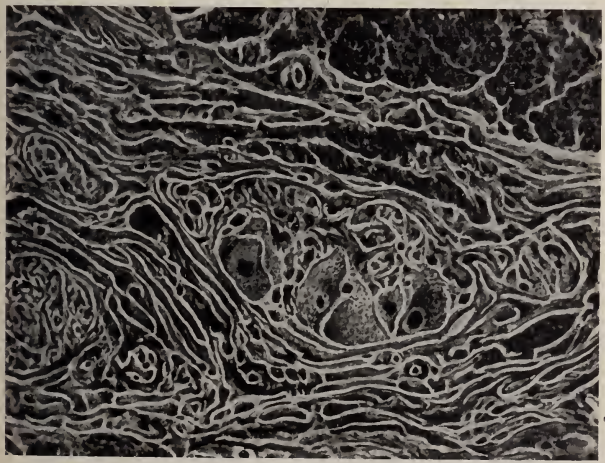

FIG. 15. Nerve cells in Meissner's plexus (plexus submucosa) displaying the typical cytoplasmic inflation and degeneration. Nissl stain, × 350.

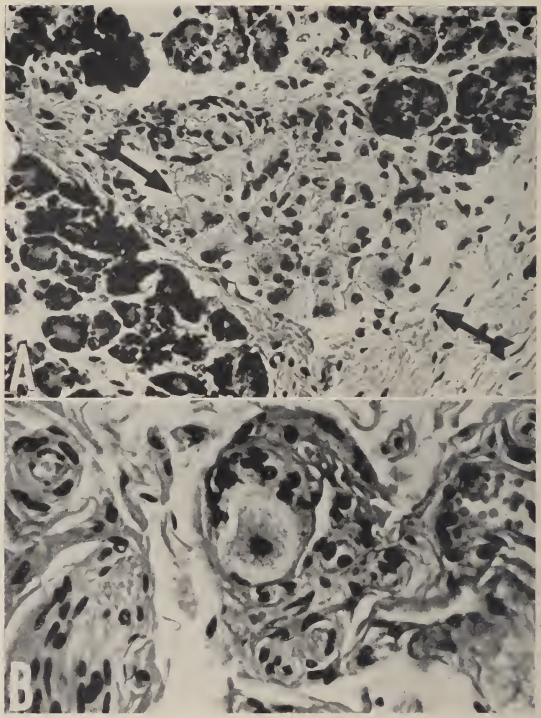

FIG. 16. A. Arrow points to a group of nerve cells in the pancreas exhibiting typical degenerative changes. Hematoxylin and eosin stain, × 365. B. A single swollen nerve cell in the wall of the urinary bladder. Hematoxylin and eosin stain, × 580.

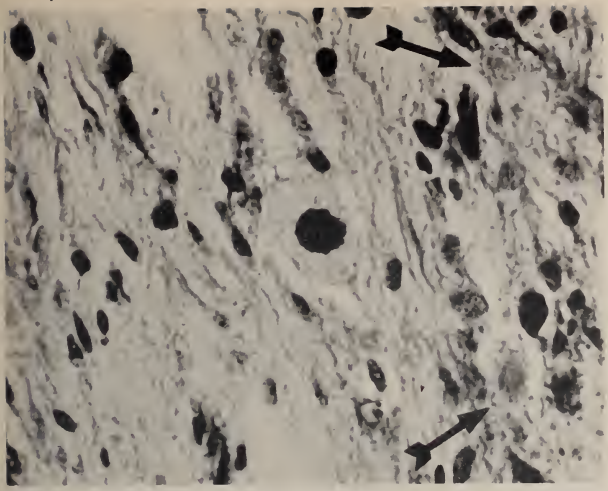

FIG. 17. Section of the posterior lobe of the pituitary, showing paucity of pituicytes, the presence of many granular globoid bodies (arrow) and a large cell, probably a nerve cell, displaying the typical alterations. Schaffer's modification of Weigert's myelin stain, × 585.

FIG. 18. Section of the posterior lobe of the pituitary body, showing various deformities of pituicytes and a large elongated cell filled with prelipoid granules. Schaffer's modification of Weigert's myelin stain, × 570.

Some of the changes in the nervous system will be stressed in the other illustrative cases.

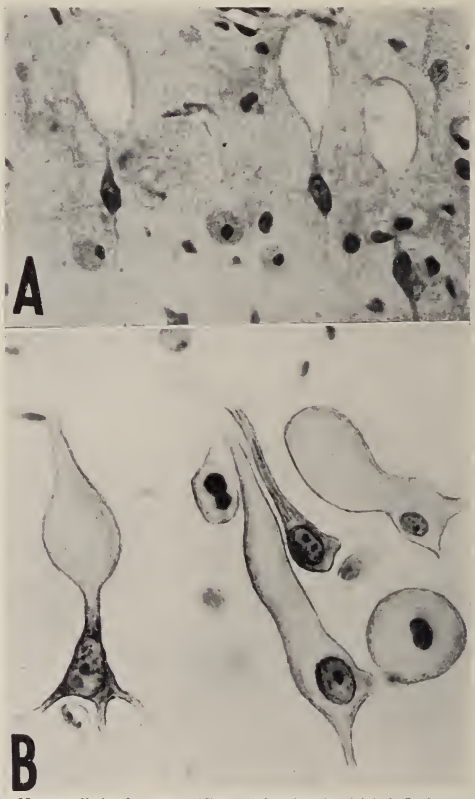

FIG. 19. A. Nerve cells in the cortex (Case 2) showing dendritic inflations and fairly well preserved cell bodies. Nissl stain, × 300. B. Section of cerebral cortex showing markedly deformed and swollen cell bodies, alongside of fairly well preserved cells with dilated dendrites. Nissl stain, × 800.

Case 2. Anatomical observations. Gross: The brain is unusually small, but retains a fairly regular gyral pattern. The gyri, however, are atrophic and the sulci are wide, some are gaping. The leptomeninges are edematous, turbid and thickened, particularly over

the fronto-parietal region. On sectioning of the brain, almost the entire white matter of the cerebrum and cerebellum is found to be gelatinous in appearance and of markedly diminished consistency.

Microscopic: The *leptomeninges* show an irregular but distinct increase in the fibrous tissue. The latter forms a meshwork which encloses numerous compound granular cells, macrophages and some round structures resembling corpora amylacea. There are no lymphocytic infiltrations or the so-called perivascular infiltrations.

The *cerebral cortex* in this case also shows the widespread nerve cell similar to that noted in Case 1. Here again, a great number of the nerve cells have lost their angular outline and have assumed a rounded or ovoid form of an unusually large size. In Nissl preparations the cytoplasm of most of the cells is devoid of tigroid substance, the nucleus appears suf-

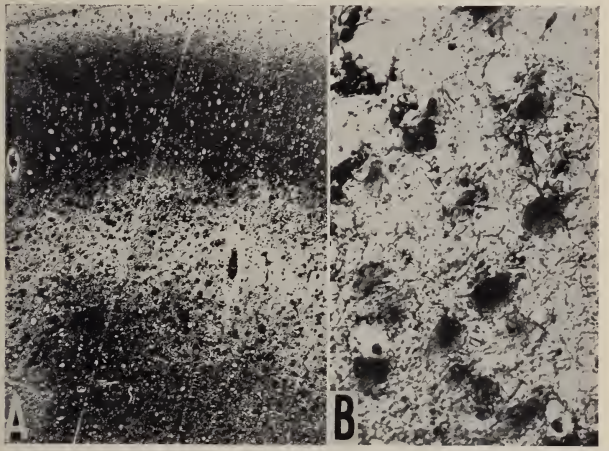

FIG. 20. A. Cerebral cortex (Case 2) showing variations in intensity of the disrupting process, most pronounced in some cortical lamellae. Cajal's gold sublimate stain (Globus' modification). B. Glial mobilization in the zone of greatest rarefaction as shown in fig. 20A.

fused and is displaced to the periphery of the cell. Some of these cells, however, revealing almost normal cell bodies, display marked inflations of the axis cylinders and the main dendrites (fig. 19). Among the nerve cells, rounded swollen glial elements are encountered in fairly large numbers. They are most numerous wherever the loss of nerve cells is greatest. Sections stained by the *Bielschowsky* method exhibit cell changes which in general correspond to those seen in Case 1. There are cells with marked inflation of the cell body and almost complete disintegration of the nucleus. The center of the cell body is filled with granular material, while the endocellular fibrillae are displaced to the periphery. A large number of glial elements are seen among the cells. They, too, are enlarged and are filled with granular material, their nuclei being displaced to the periphery. In *scarlet red* preparations the accumulation of neutral fat is similar in distribution to that seen in the cerebral cortex of Case 1. Preparations stained by the *Marchi* (osmic acid) method reveal alterations of a character and intensity corresponding to those noted in scarlet red stained

sections. Here the nerve cells show only a light, dust-like gray coloration of the cytoplasm, while the glia cells are laden with dark gray, almost black, coarse granules. With Schaffer's modification of Weigert's myelin stain the cerebral cortex exhibits cell alterations similar to those seen in Case 1, but also shows the specific granules in the inflated dendrites and axis cylinders. These granules stain more intensely in the glia.

The paucity of nerve cells due to disintegration and the glial mobilization in this case vary in intensity in the several cortical layers. This is readily recognized in preparations stained by the modification of the Cajal gold sublimate method (fig. 20). The entire cortex appears as a densely stained mass because of the large deposits of the prelipoid granules in the affected cells, but nevertheless several lighter strips interrupt this mass. These zones, when studied in preparations stained by the Nissl method, appear almost completely devoid of nerve cells and are the seat of a fine fibrous network, enmeshing many protoplasmic astrocytes and an occasional compound granular cell. It is quite probable that these strips represent zones in which the disease process, being of longer duration, resulted in the dis-

FIG. 21. Cerebellar cortex (Case 2) showing narrowing of the granular layer. Nissl stain, × 55.

integration and disappearance of nerve cells, their place being taken in part by protoplasmic glia cells.

The cerebellar cortex exhibits a marked atrophy of the folia, due to narrowing of the granular layer with an almost complete disappearance of the Purkinje cells (fig. 21). The few remaining Purkinje cells show the characteristic changes of the disease: inflation of the axis cylinders and the dendrites, displacement of the intracellular fibrillae and of the nucleus, and a marked irregularity in the thickness of the axis cylinders (fig. 22). There is also a distinct loss of the moss and climbing fibers with a reduction in the fiber reticulum about the Purkinje cells. Heavy cytoplasmic deposits of the prelipoid substance are revealed by the special stains, as well as marked glial proliferation.

Cerebral subcortex: The gelatinous consistence of the white substance noted on gross inspection of the brain, as microscopic study indicates, is due to a vast and diffuse process of demyelination. In Weigert preparations the white substance appears as light (smoky) gray with but an occasional darker island of somewhat better preserved myelinated fibers. Preparations stained for fat (scarlet red) show that large areas of the subcortex are replaced by dense masses of compound granular cells filled with fat. These cells are densest at the periphery of blood vessels (fig. 23). There is but a mild proliferation of fibroblastic glia, while, where the compound granular cells are more numerous, the fibrous glia cells are

almost totally absent. The axis cylinders are found in various stages of disintegration; they are reduced in number and exhibit disease alterations. The latter are best displayed in Bielschowsky's preparations, and recognized as oval or bulbous inflations with marked disturbance of the fibrillary structure (fig. 24).

Cerebellar subcortex: Here the changes are similar to those found in the cerebral subcortex. There is wide and intense demyelination and large accumulations of compound granular cells laden with fat.

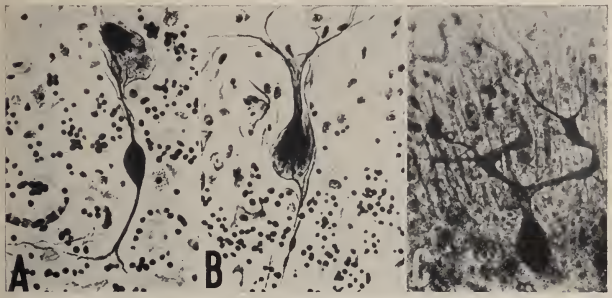

FIG. 22. Purkinje cells showing typical alterations (Case 2), see text. A. Bielschowsky stain, × 580. B. Bielschowsky stain, × 580. C. Cajal's gold sublimate method, × 580.

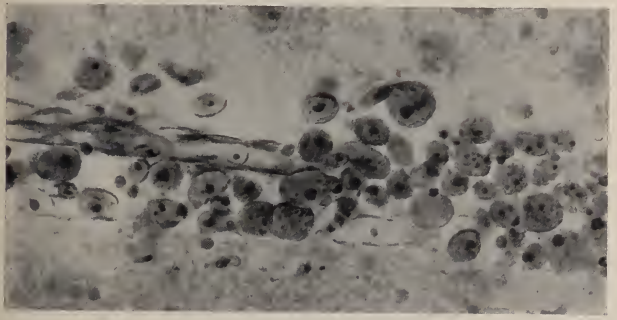

FIG. 23. A vessel surrounded by a large array of compound granular cells (Case 2). Hortega's silver carbonate stain (Globus' modification), × 580.

Brain stem: The cell alterations here are similar to those noted in the nerve cells elsewhere in the brain. The fibers, particularly in the cortico-spinal system and the deep and superficial pontine fibers, are completely deprived of myelin and are surrounded by numerous compound granular cells. In striking contrast to this is the preservation of the myelin coating in other systems, such as the medial and lateral lemnisci, the superior cerebellar peduncles, and the posterior longitudinal bundles (fig. 25).

FIG. 24. Drawing illustrating several types of axis cylinder disintegration. *a*. A distended axis cylinder containing fine granular deposits. *b* and *c*. Distended axis cylinders retaining a fibrillary structure. *d*. A swollen axis cylinder filled with coarse granular material. *e, f, g, h*. Axis cylinder distentions containing distinct fibrillary structure, some having the appearance of terminal bulbs (*g*). *i*. An axis cylinder with a bulbous swelling, winding between two compound granular cells.

FIG. 25. Section of the anterior portion of the pons (Case 2) showing complete demyelination of the pontine fibers and the corticopontine and corticospinal tracts. Weigert's myelin stain.

Summary: This case, in general, also typifies the infantile form of amaurotic family idiocy, exhibiting in addition a widespread affliction of the nerve cells and marked inflation of their processes. The intense cerebellar involvement, and the vast myelin degeneration in the subcortex in both cerebrum and cerebellum, are also striking departures from the more typical instances.

Case 3. Anatomical observations. Gross: The brain in all its subdivisions seems reduced in size and the cerebral gyri appear somewhat more numerous. The leptomeninges are somewhat thickened and dull. Sectioning of the brain discloses an increased consistence of both cortex and subcortex with the gray matter poorly demarcated from the white matter. The ventricular system is enlarged (fig. 26).

Microscopic: The nerve cell alterations in the cerebral cortex in this case are more like those found in Case 1, for here also they are restricted mainly to the cell body with the

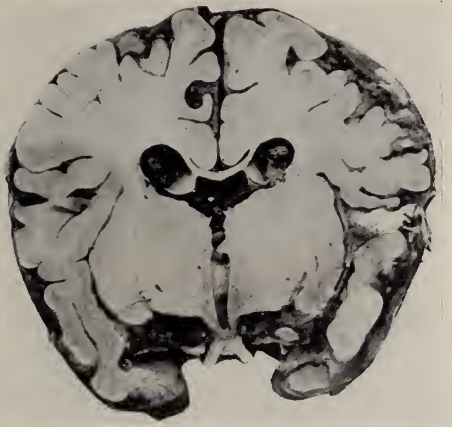

FIG. 26. Coronal section of the brain (Case 3)

swelling of the axis cylinders being somewhat less common, while swollen dendrites are quite frequent (fig. 27 A). In silver preparations in this case, the intracellular fibrillae, in contrast to their arrangement in Cases 1 and 2 are quite well preserved in the center of the cell where they form a coarse network (fig. 27 B). The cytoarchitecture of the cerebral cortex, because of the great loss of nerve cells, is very disturbed, without, however, displaying a predilection for any special layer. The inner granular layer seems to be most disturbed and in the calcarine area all of the subdivisions of lamina IV are affected in a similar way. Schaffer's modification of the Weigert method impregnates only isolated granules which have a pale hue; such is also the case with sections stained by the Cajal gold sublimate method. Scarlet red stained preparations exhibit nerve cells which take only a light pale pink fine granulation, while the few compound granular cells show a coarse and deep red granulation. The latter is seen in large numbers, especially in lamina I, as well as in the perivascular spaces of the vessels of the cortex. A totally different picture is obtained by the Marchi method. Here grayish black or black granules in the nerve cell body as in the

inflated dendrites mark the presence of large quantities of the prelipoid substance. A similar, but more intense, reaction is exhibited by the compound granular cells. An intense glial mobilization is noted throughout the cerebral cortex as well as in other gray masses

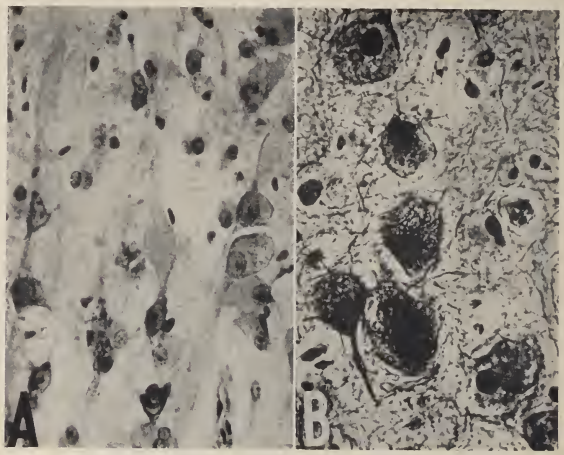

FIG. 27. A. Nerve cells in the cortex (Case 3) showing typical alterations. Nissl stain, × 300. B. The reticulum-like formation of the endocellular fibrillae in the cells of the cortex (Case 3). Bielschowsky silver stain, × 400.

FIG. 28. Glial arrangement about a blood vessel (Case 3). Cajal's gold sublimate stain (Globus' modification), × 800.

as large glia cells with well defined fibrous processes are encountered. Many of these processes can be traced to blood vessels where they form sharply outlined glial limiting membranes, while elsewhere single nerve cells are embraced by rampant glial elements. At times a monstrous glia cell with numerous protoplasmic processes embraces a granular substance, probably remnants of either nerve cells or glial structures (fig. 29).

The entire white substance is the seat of a widespread sclerotic process, being densely infiltrated with protoplasmic and fibroblastic glia cells (fig. 28). Isolated compound granular cells are scattered in the tissue. In some areas, especially in the corpus callosum, in the fornix, in certain parts of the thalamus, in the brain stem and in the corpus restiforme,

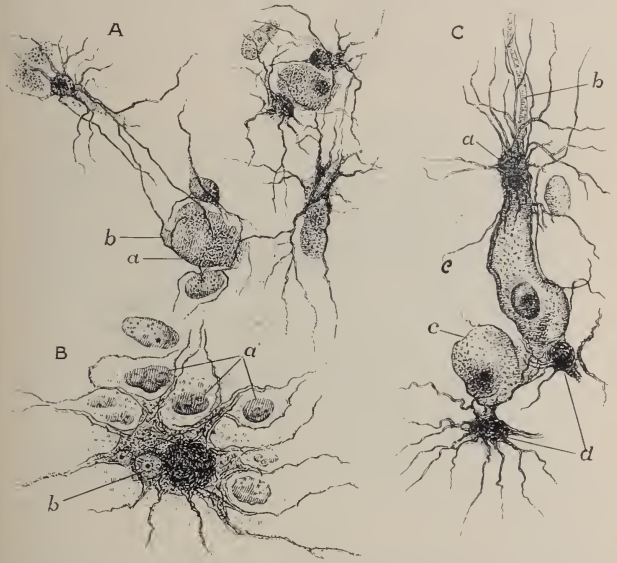

Fig. 29. Drawing illustrating glia elements in the cerebral cortex (Case 3). A. A nerve cell (a) completely embraced by glial processes (b). B. A monstrous glia cell with tremendously developed protoplasmic processes, enclosing or grasping rounded granular bodies (a), some having the appearance of a nucleus (b). C. Individual nerve cells (c) embraced by rampant glial forms, some of which send their branchy processes up on the dendrites (b).

the degenerative character of the process is accentuated by the presence of large accumulations of fat laden compound granular cells (fig. 30). There are some areas consisting mainly of enormous masses of compound granular cells within which smaller vessels can be discerned, whose perivascular spaces are filled with fatty waste products.

Bielschowsky preparations disclose alterations similar to those found in Case 1, but less advanced, though in some selected areas there are encountered more intensely disintegrated axis cylinders. The long projectile tracts in which axis cylinders on the whole are quite well preserved, occasionally reveal swollen axons.

Marked demyelination of the subcortex is noted particularly in the frontal area, but

also in the temporal region, the corpus callosum and the fornix. In the diencephalon there is fairly marked loss of myelin with the thalamus having been spared to some extent. Peculiarly enough, the pyramidal tracts are well myelinated. The striatum shows only mild myelination with the pallidum assuming a more than normal transparency. The optic tracts (fig. 31) show in their entire course rather good preservation of myelin.

The cerebellar cortex discloses alterations similar to those noted in the other cases; the Purkinje cells are markedly reduced in number, the remaining cells show the same alterations as those in Cases 1 and 2.

The cerebellar subcortex in myelin sheath preparations reveals a widespread demyelination, while the brachium conjunctivum and the restiform bodies are relatively intact. In the pons, the distinctly demyelinated fronto- and temporo-pontine tracts stand out against the well preserved lemniscus and the pyramidal tracts. The olivary fibers are also well preserved. In the medulla oblongata there are no definite medullary sheath changes, while the Marchi and scarlet red preparations disclose compound granular cell accumulations in the spino-cerebellar tracts.

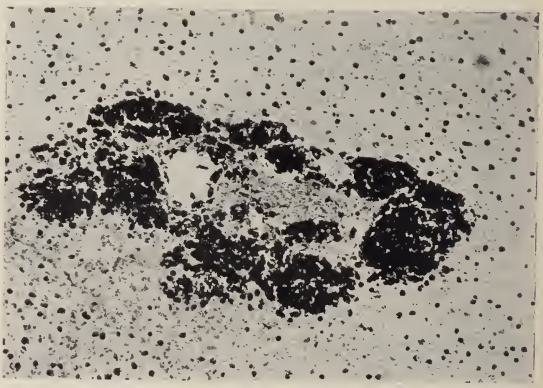

FIG. 30. Large focal accumulation of fat in the subcortex about a vessel and an adjacent area of disintegration (Case 3). Herxheimer's scarlet red stain, × 90.

Summary: In a 25 months old child, with the characteristic symptoms and signs of the infantile form of amaurotic family idiocy, the ubiquitous and typical nerve cell changes were accompanied by a marked sclerotic process. The cortical architecture was markedly disturbed and resulted in localized development of a status spongiosus. A special preference for certain layers could not be established. In this instance, in contrast to Cases 1 and 2, there was found an extensive glial proliferation in the character of hypertrophic protoplasmic and fiber forming glia cells. The white matter in the cerebrum and cerebellum revealed a diffuse and marked process of demyelination affecting particularly the frontal, temporal, and occipital lobes. The thalamus, the island of Reil, the corpus callosum, the fornix, the corpus striatum, corpus Luysii, and the lateral geniculate body were also markedly affected by this process. The cerebellar white matter was also atrophied and was poorly myelinated. Extensive areas

crowded with compound granular cells were found in the white matter. The spino-cerebellar tracts were found to be in the process of acute softening.

A FEW REMARKS IN COMMENT ON THE INFANTILE VARIANT OF AMAUROTIC FAMILY IDIOCY

There are several clinical features disclosed by the members of the foregoing group of eleven cases which deserve mention. There is the rather striking fact than ten of the eleven infants in this group were females. Sachs and Hausman (21) recorded a larger number of instances of amaurotic family idiocy and found also in their patients a preponderance of females over males in a ratio of approxi-3 to 1. This, of course, is not without significance, but its true meaning can only be disclosed on study of a larger material by those who are better prepared to solve such problems. The fact that all the cases were of Jewish parentage,

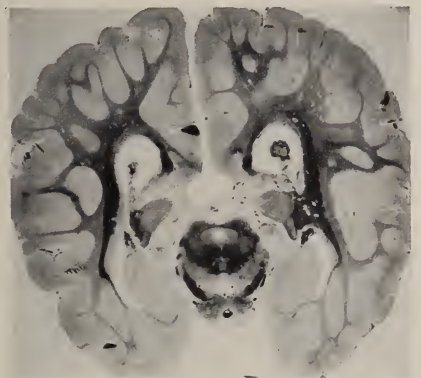

FIG. 31. Coronal section of the brain (Case 3), showing preservation of myelin in terminal course of the optic tracts as well as in the long projection tracts in the midbrain.

requires little comment, since the affliction is known to be prevalent among Jewish children.

Consanguinity in this group of cases was the exception, while a familial predisposition was present in a large quota (in five) of the cases.

There was a moderate variability in the span of life of the cases recorded in the appended table, and one case (Case 11) in which the onset of symptoms occurred rather late (at the age of one year), may be considered as an instance which approximates the late infantile form of this disease. On the other hand, in two instances the onset of the affliction could not be determined clinically since the affected children did not seem to make good progress since birth. Thus, they could be grouped with the newly described variant, the congenital form of amaurotic family idiocy (18).

Little need be said at this point about some variations in the anatomical features exhibited by the foregoing group of cases. As will be pointed out else-

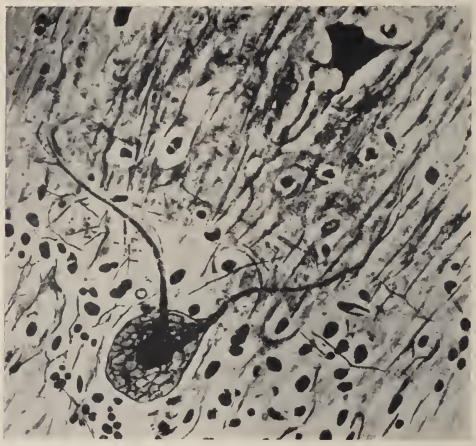

FIG. 32. A Purkinje cell showing the reticular cytoplasmic formation (Case 3). Bielschowsky silver stain, × 600.

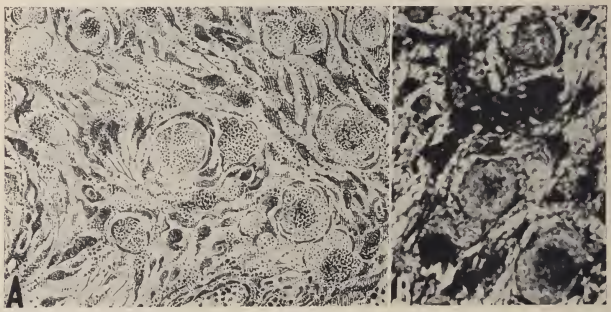

FIG. 33. A. Drawing illustrating the structure of the posterior lobe of the pituitary body showing many large globoid, granular bodies and swollen pituicytes. B. Photomicrograph exhibiting the character of the large globoid bodies illustrated in fig. 33A.

where, such variations are little more than an expression of a stage in the development of the disease. Thus, the presence or absence of inflation of the cell processes, in one or another case, does not alter the basic character of the disease,

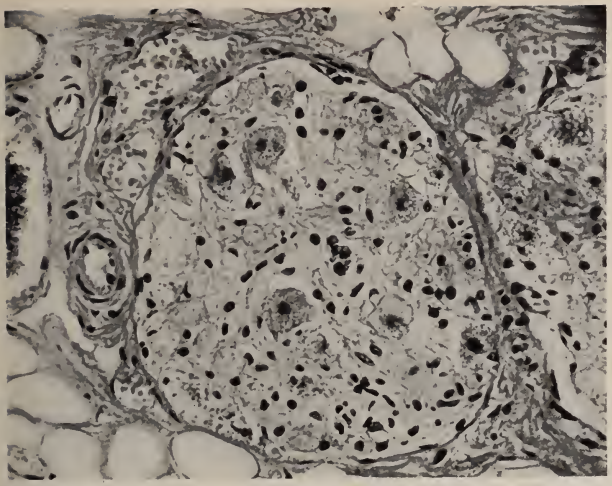

FIG. 34. Typical alterations in nerve cells of a small ganglion situated at the periphery of the adrenal.

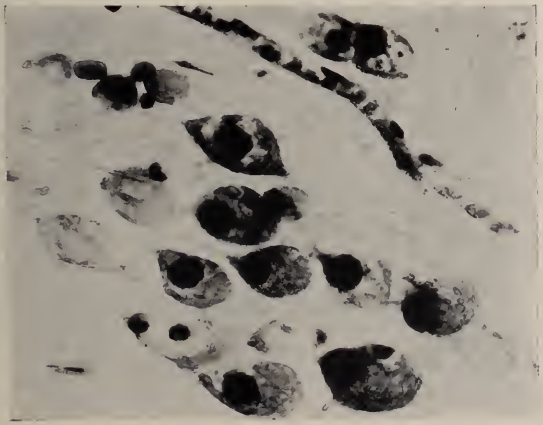

FIG. 35. Nerve cells in the gray matter (Case 3) showing fairly well preserved nuclei, surrounded by inflated and vacuolated cell bodies devoid of tigroid substance. Nissl stain, × 740.

as long as the typical cell body changes are in evidence. The same holds true for the axis cylinder changes and for the degree and extent of demyelination.

The ubiquitous character of the disease is further emphasized by the disclosure of typical changes in the nerve cells scattered through the abdominal viscera (pancreas, gastro-intestinal tract, urinary bladder, adrenals) and of the cell alterations in the posterior lobe of the hypophysis, an organ of neuroectodermal derivation.

On the other hand the anterior lobe showed no obvious pathologic alteration, except for a deep staining reaction with the Schaffer method, the cells being densely filled with rough granules. Other glands of internal secretion particularly the thyroid, thymus and the adrenals were studied and failed to disclose pathologic changes, such as were claimed by some observers and recently by Marburg (22).

In the pineal body no changes were noted except for an occasional stray nerve cell exhibiting the typical changes.

THE LATE INFANTILE FORM OF AMAUROTIC FAMILY IDIOCY

Attention was called by Jansky (23) to this variant of the disease; it was studied especially by Bielschowsky (24), Hassin (25), and others. The affliction first becomes manifest in the third and fourth years of life and is marked by the appearance of optic nerve atrophy unaccompanied by the cherry red spot in the macula which is so characteristic of the infantile type. In this form of the disease, unlike the infantile variant, there is no racial predilection and it runs a rather slow course with a gradual process of mental disintegration. The physical decline and neurologic manifestations such as decerebrate rigidity and bulbar symptoms appear rather late in the clinical course, at a stage close to the fatal termination, which occurs usually about the end of the fourth year. This variant is now regarded as a transition from the infantile, on the one hand, to the still later form, the juvenile (Spielmeyer-Vogt), on the other. This merging of types becomes more obvious in instances in which the course of the late infantile form of the disease is protracted so as to extend over a period of three or more years. Such a mergence is still more obvious between the infantile and the late infantile forms. This is well demonstrated by Case 11, a member of the foregoing group of examples of the infantile form.

Anatomically, the disease process here is characterized by features almost indistinguishable from those encountered in the infantile form. There is the ubiquitous cell affliction with cell body swelling, inflation of the processes and elaboration of the prelipoid granules. The involvement of the cerebellum and subcortical (both cerebral and cerebellar) white matter has been stressed by several investigators as a departure from the typical infantile variant of the disease.

Clinically, deviations from the typical picture of the infantile form are here more numerous. Occasionally these are so pronounced as to lead the examiner astray from the true diagnosis, an error which is rectified only by post-mortem study. Such was the case in an instance reported by Hassin (25) whose histologic studies established the diagnosis in a seven year old girl, who developed signs of

regression at the age of three years, with the disintegration, both mental and physical, progressing slowly during the following four years. In view of the ophthalmologist's report on the fundi examination which read: "probably postneuritic, secondary to papilledema with visible choroid vessels; four or five tuberculous nodules were seen on the choroid of the right retina. The impression is that we are dealing with a Tuberculoma," the diagnosis of a tumor, probably in the region of the sella turcica, was made by the clinician. The child died and the brain was submitted to Dr. Hassin for neuropathologic studies. He reported (25) in the main the disclosure of "widespread cellular changes typical of amaurotic family idiocy, vacuolated cells containing amorphous material, and atrophy of the cerebellar layers . . . and absence of secondary degeneration in the white substance of the brain and spinal cord."

THE JUVENILE FORM OF AMAUROTIC FAMILY IDIOCY

This variant of the affliction described originally and simultaneously by Spielmeyer (26) and Vogt (27) and recently by Jervis and Roizin (28) makes its appearance during the early period of the second dentition and is typified also by a triad of signs and symptoms, consisting of blindness, spastic paralysis, and progressive disintegration of the intellect. However, the cherry red spot in the macula, common in the infantile form, is absent, and the optic atrophy noted in the late infantile form is less pronounced or may be altogether absent. Instead, there is another pathologic alteration in the visual apparatus, commonly recognized and designated as *retinitis pigmentosa*. The racial predilection in this form is also absent. Histologically, swelling of the nerve cells is less ubiquitous, but in the cells affected, there is the characteristic deposition of the prelipoid substances and the displacement of the intracellular fibrillae.

ILLUSTRATIVE CASE

The following instance of the juvenile form of this disease is the only case of this type I had the opportunity to study anatomically. I have already reported it at greater length in an earlier paper (15), and shall briefly review the more striking clinical and histological observations. Of great significance is the family history of the patient, which points definitely to the familial character of her malady. Two siblings of the patient and an aunt on the paternal side were blind and inmates of an institution for mental defectives. Another sister died of epilepsy in a State Hospital, while still another sister, who developed normally up to the age of twelve years, began to regress. Motor hyperactivity of a type suggestive of striatal dysfunction, psychotic manifestations and pigmentation of the retina developed shortly thereafter (a triad of symptoms: blindness, mental deterioration, and convulsive seizures), and she died at the age of twenty-one years. At post-mortem examination the only striking finding recorded was marked atrophy of the optic thalamus.

Personal history: The patient had apparently normal development as a child. Her years of adolescence were spent as an inmate in an institution for the blind. In the course of time she began to display progressive mental deterioration and she was transferred to an institution for mental defectives. She soon began to show marked conduct disorders

and psychotic manifestations, which brought her to a State Hospital for the Insane. Epileptiform seizures, disarthric speech and disorderly conduct soon made their appearance. The optic discs became atrophic and pigmentation which in character and distribution was typical of *retinitis pigmentosa* was noted. The epileptiform seizures became more frequent

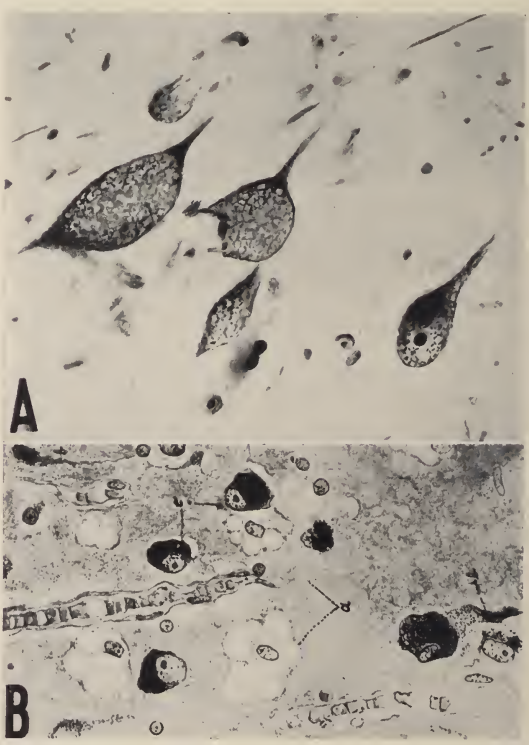

FIG. 36. A. Cell forms in the cortex of a case of the juvenile form of amaurotic family idiocy. Nissl stain, × 800. B. Neutral fat accumulated in nerve cell of the juvenile form of amaurotic family idiocy.

and were accompanied by progressive decline in the physical and mental status. She died at the age of twenty-one years.

Anatomical observations. Gross: The brain exhibits no significant changes.

Microscopic: The leptomeninges are apparently intact and show little more than a few macrophages in the pia-arachnoid space.

Cerebral cortex: Throughout the central gray matter there are present the characteristic cell alterations, with swelling of the cell body and occasional inflation of the dendrites. The nerve cells in general are markedly reduced in number. Highly striking is that alongside of diseased cells, there are often encountered fully preserved cells (fig. 36 A) which have retained their normal form and a normal content of tigroid substance. Bielschowsky preparations exhibit the disappearance or displacement of the endocellular fibrillary structure and prelipoid granules within the cytoplasm. Granules stained rather deeply with the Herxheimer stain (scarlet red) for fat, are quite numerous in the affected nerve cells (fig. 36 B), but are sparce in the corresponding compound granular cells. In Marchi (osmic acid) preparations the nerve cells contain no stainable granules. In sections stained by the Schaffer method, the nerve cells acquire a light gray hue (fig. 37) while the compound granular cells stain somewhat darker. The gold sublimate stain of Cajal, on the other hand, gives results which are similar to those noted in the infantile form of this disease.

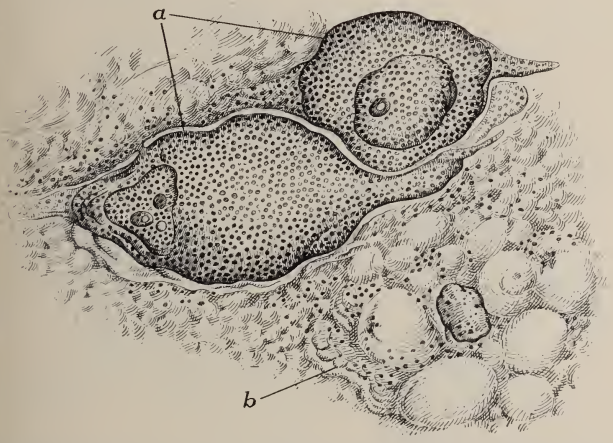

FIG. 37. Drawing of nerve cells (a) in the gray matter of a case of the juvenile form of amaurotic family idiocy, and of a mulberry glia cell (b). Schaffer's modification of Weigert's myelin stain.

An unusual form of glia cells (the mulberry cell) is noted among other cellular elements. They are unusually large, contain a large centrally situated nucleus and many large vacuoles (fig. 38). In silver preparations, they are noted to enclose deeply staining spheroid bodies.

Other glia cells are not numerous; there is some increase in the number of protoplasmic glia, in the cortex, and here and there an occasional glial rosette may be encountered about disintegrated nerve cells.

The cerebellum shows narrowing of the granular layer, widespread loss of Purkinje cells, the remaining Purkinje cells exhibiting the typical alterations (fig. 39). Axis cylinder changes are not encountered.

Summary: This case, therefore, is one of juvenile amaurotic family idiocy with accentuation on the hereditary and familial factors. In the fundi, the

cherry red spot was absent, but there was a distinct optic atrophy and alterations in the nature of *retinitis pigmentosa*.

Anatomically, throughout the whole gray matter of the central nervous system there are found typical nerve cell changes with a rare occurrence of inflation of their processes. The prelipoid substance yields an extensive scarlet red reaction, a less extensive gold sublimate reaction, only faint staining with Schaffer's method and a negative reaction with the Marchi method. The glial reaction is light and of the protoplasmic variety only with a limited tendency towards

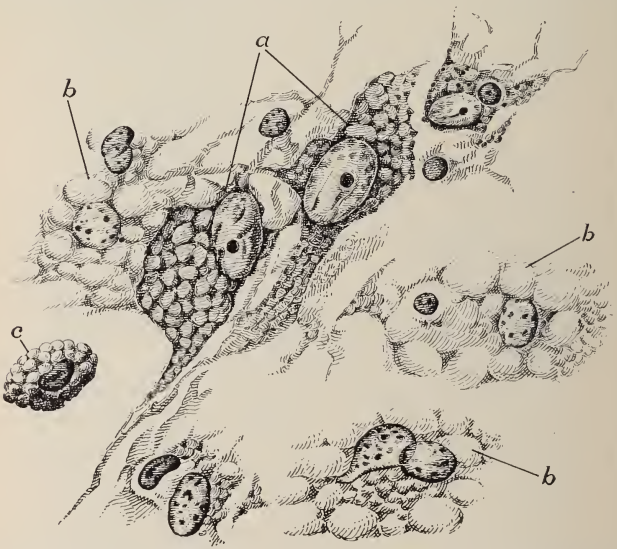

FIG. 38. Drawing illustrating nerve cells (a) mulberry glia cells (b), and a compound granular cell (c) in the juvenile form of amaurotic family idiocy. Bielschowsky silver stain.

formation of compound granular cells. Mulberry-like forms of glia are striking by their large size and enclosures. The cerebellum is poor in Purkinje cells and presents an atrophy of the granular layer. The nerve cell process is not ubiquitous in the cortex and in the rest of the gray centers displays everywhere focal variations in the intensity of the disease process.

THE ADULT FORM OF AMAUROTIC FAMILY IDIOCY

To the three foregoing forms, another rare variant of this disease may be added. There are only a few instances of this in the literature. The case described by Kufs (29), which serves as a good example of this form of the disease is generally

characterized by a late onset, usually in the beginning of the third decade of life. Loss of vision, development of *retinitis pigmentosa*, and optic atrophy without the characteristic cherry red spot, are its prominent signs and symptoms. They are accompanied by progressive mental depreciation. Muscular rigidity, incoordination and pyramidal tract signs, as well as bulbar signs and symptoms are usually absent. An exceptional case of the adult form of amaurotic family idiocy in which the above manifestations were present, but which lacked visual impairment, the most essential element in the typical constellation of signs and symptoms, was described by Meyer (30). His patient began to exhibit clinical manifestations of the disease at the approximate age of eighteen years. At first there appeared coarse tremors of the arms. This was soon followed by disturbances in articulation and swallowing, and by gradually advancing mental depreciation. When seen at the age of twenty-six years, she exhibited bulbar

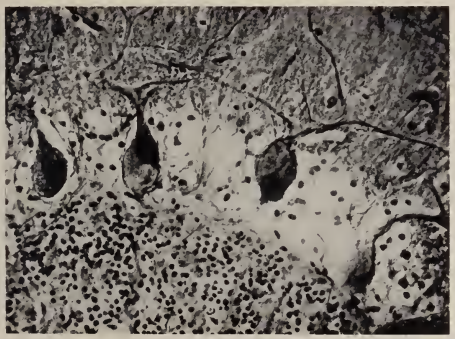

Fig. 39. Purkinje cells in the juvenile form of amaurotic family idiocy displaying typical alterations. Bielschowsky silver stain, × 300.

symptoms, signs of both pyramidal and extrapyramidal dysfunction, and manifestations of mental deterioration The diagnosis was established only on histologic study of the brain, which disclosed the characteristic cellular changes, most pronounced in the basal ganglia, and particularly in the thalamus, in certain cellular groups of the tuber cinereum and in the substantia nigra. With this case in mind it may be recalled that in the herein reported case of the juvenile form of amaurotic family idiocy (Case 12) a sister exhibited clinical manifestations which were strikingly similar to those displayed by the patient of Meyer. There, too, at autopsy marked atrophy and disintegration of the thalamus were disclosed.

THE CONGENITAL FORM OF AMAUROTIC FAMILY IDIOCY

Of great significance in the study of this disease are the observations on a case recently described by Norman and Wood (18). Their patient was an

eighteen day old female infant. The family history contained a few relevant facts: the father's brother was certified as a mental defective and an aunt of the father was suffering from unspecified mental trouble. The infant was a full term baby. A few days after birth she became slightly blue during feedings and soon after began to regurgitate fluids. A catheter was passed down the esophagus, but there was no obstruction. During the last five days of her life blood was found in the napkins. The infant died on the eighteenth day of her life with the cause being, at first, obscure. At autopsy bilateral hemorrhage in the renal pyramids was found. The brain was unusually small and the convolutional pattern showed marked underdevelopment. Microscopically, the nerve cells showed the typical alterations characteristic of amaurotic family idiocy with numerous atypical nerve cells exhibiting extreme distension. The intracellular lipoid substance was described as being resistant to solvents.[7] These alterations were found throughout the cerebellar and cerebral cortices. The glial elements showed also "lipoid abnormalities," and a general increase in number. Myelination was retarded throughout the nervous system and "heavy deposits of extracellular doubly refractile crystals of cholesterol esters were present in the white matter" of the brain. There was severe olivo-cerebellar atrophy. The viscera showed also evidence of lipoid storage in the reticulo-endothelial system with histo-chemical reactions of the deposited substance, resembling those of the nerve cell granules.

Thus, the authors definitely established the character of the disease as a variant of amaurotic family idiocy. It was associated with lipoid storage like that found in Niemann-Pick disease and disclosed some differences in the chemical behavior of the lipoid deposits. The early appearance of the disease and the presence of gross abnormalities led them to the conclusion that theirs was an instance of a "hitherto undescribed variety of lipoidosis" for which they suggested the name of congenital form of amaurotic family idiocy.

AMAUROTIC FAMILY IDIOCY ASSOCIATED WITH NIEMANN-PICK DISEASE

Of major importance is the discovery of cases in which the nervous system exhibits the typical cell changes of the infantile form of amaurotic family idiocy and which reveals also the signs and pathologic findings of Niemann-Pick disease: hepatosplenomegaly with lipoid histiocytosis. Here, too, the disease begins to unfold itself in the early months of infancy but is first recognized by the enlargement of the liver and spleen, and the brownish discoloration of the skin. Somewhat later the manifestations of cerebral involvement become apparent. As in the other infantile form of amaurotic family idiocy the child first appears to make fairly good progress in development and then quite suddenly

[7] Chemical questions involved in the study of amaurotic family idiocy were avoided throughout this article. Such discussion was left to others who are better equipped to deal with the problems. Thus, the author refers the reader to the articles by Dr. Sobotka and Dr. Sperry for views relating to the chemical nature and variations of the lipoids so prominent in this disease, and to the article by Norman and Wood (18) for their observations on the chemical peculiarities of the lipoid deposits in their case.

begins to regress both physically and mentally. The clinical course then follows the pattern of a typical instance of amaurotic family idiocy, often exhibiting fairly typical macular changes. Its clinical and anatomical findings are exemplified by those noted in the following case.

ILLUSTRATIVE CASE

Case 12. History: S. H., a female child, was brought to the hospital at the age of ten months. Her family history was negative for consanguinity. She was a full term, normal baby, weighing, however, only $4\frac{3}{4}$ pounds. She was breast fed until the age of seven months, when weaning was begun. Feeding of the child by bottle was difficult and a few days after she was weaned she began to vomit. In the course of the next few weeks she began to display mental regression, became apathetic and inactive. Shortly before she entered the hospital she began to cough and became febrile.

Examination: The child was marantic, the head was large, the fontanelles were wide open and the sclerae were blue. The skin had a general brownish tinge. The liver and spleen were enlarged (fig. 40). The pupils reacted to light. The fundi displayed yellowish nerve heads, a large oval macula, grayish in color with a central large "cherry red spot."

FIG. 40. Photograph of an infant (Case 12; Niemann-Pick disease) with the lower limits of the enlarged liver and spleen marked on the abdomen.

She was unable to sit up, but could support her head. She apparently could hear as she would respond to noises. She did not grasp for objects.

A blood examination disclosed, among other findings, a white blood count of 16,000 of which 51 per cent were polymorphonuclear leucocytes, and 49 per cent lymphocytes, 75 per cent of the latter had a vacuolated cytoplasm.

Course: In view of the presence of the macular changes, the spleno-hepatomegaly and the vacuolization of the lymphocytes in the blood, the diagnosis of a combined Niemann-Pick disease was made. Splenic puncture yielded tissue which was found to contain the histiocytes characteristic of Niemann-Pick disease.

The patient's condition declined gradually. She was taken home, but returned about four months later, when she suddenly lapsed into a deep stupor. She died soon after admission with signs of pneumonia.

Anatomical observations. Gross: The liver and spleen are markedly enlarged, the mesenteric lymph nodes are prominent. The adrenals are normal in size and shape, the medulla is somewhat narrower than normal. The pancreas is slightly larger than normal. The kidneys are normal in size and weight. The thyroid gland is negative. The bone marrow is somewhat pale and creamy.

The *brain* weighs 314 grams. It is small and its consistence is rubbery. The meninges are somewhat dull. The convolutions are normal.

Microscopic: Lungs: the alveoli are filled with Niemann-Pick cells. *Adrenals:* the cells

of the cortex are filled with lipoid material. *Pancreas:* there are no changes. *Kidneys:* droplets, probably particles of Niemann-Pick cells are found within the glomeruli. *Thyroid, ovaries, skin, muscle tissue:* there are no changes. *Liver:* there are many Niemann-

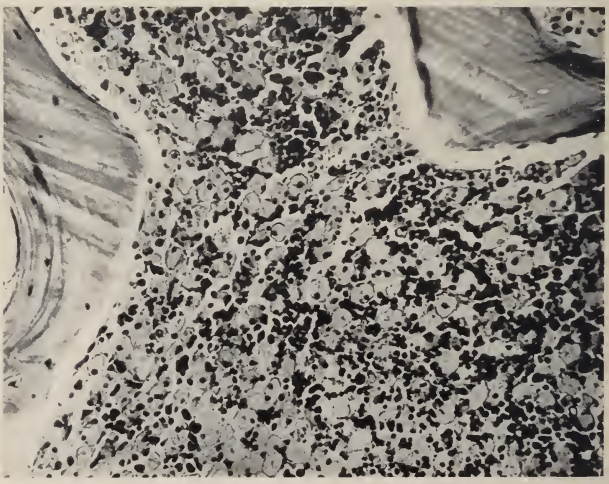

FIG. 41. Bone marrow (Case 12; Niemann-Pick disease) exhibiting numerous histiocytes typical of the disease.

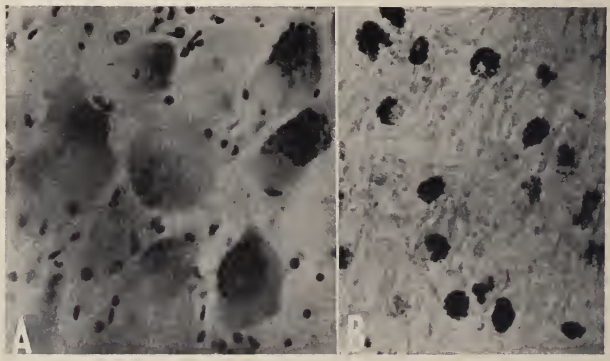

FIG. 42. A. Cell alterations in the cortex (Case 12; Niemann-Pick disease). Nissl stain, × 520. B. Compound granular cells filled with neutral fat (Case 12; Niemann-Pick disease). Herxheimer's scarlet red stain, × 520.

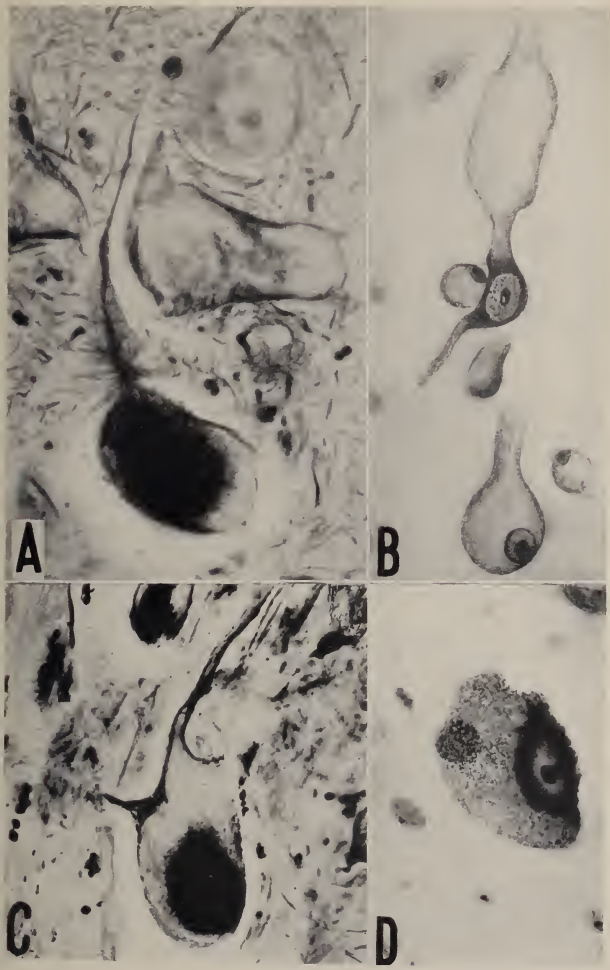

FIG. 43. Cell alterations in various parts of the cerebral and cerebellar cortex and the brain stem. (a) Hypoglossal nucleus; (b) cerebral cortex; (c) brain stem; (d) cerebellum (Purkinje cells). Nissl stain, × 580.

Pick cells in the intercellular spaces; the liver cells are often compressed and vacuolated. With Sudan stain the Niemann-Pick cells assume a light pink color, the liver cells remain unstained; with the Smith-Dittrich method the Niemann-Pick cells stain faintly. *Spleen:* Niemann-Pick cells are also found here. *Lymph nodes:* almost the entire lymph tissue is replaced by aggregations of Niemann-Pick cells. *Bone marrow:* extensive infiltration by Niemann-Pick cells (fig. 41).

Brain: The study of numerous sections taken from various regions of the cerebral and cerebellar cortex and the gray matter of the spinal cord disclose widespread changes characteristic of amaurotic family idiocy (figs. 42 A and 43).

Comment: No qualitative difference can be detected between this combined form of Niemann-Pick disease and amaurotic family idiocy in the nature of the disease process affecting the nervous system. The cell alterations, to some extent, are more pronounced than those encountered in cases of the infantile form of amaurotic family idiocy unassociated with Niemann-Pick disease. Another feature which deserved mention is the presence in the cortex of a large number of compound granular cells filled with neutral fat (fig. 42B).

GENERAL COMMENT ON THE ANATOMICAL AND CLINICAL INTERRELATIONSHIP OF THE SEVERAL VARIANTS OF THE DISEASE

From the foregoing description of the histological findings in the several forms of amaurotic family idiocy, it is quite apparent that they constitute variants of the same disease entity. This is well shown by the specific nerve cell changes, which serve as the anatomical link between the several variants. Conversely some differences are exhibited by these variants and are expressed by the intensity of the staining reactions and the extent of the distribution of the so-called prelipoid granules; in the degree and extent of dendritic swelling; and by the intensity of glial reactions. These differences, in a way, justify the subgrouping of the disease but do not vitiate the concept of its unity.

Indeed, while minute studies in certain cases may often disclose exceptional deviations from the typical pathology of clinical pictures, they nonetheless fail to establish sharp boundaries between a given case under investigation and other members of the entire group. Even in such instances the fundamental disease process is in the foreground, displaying the specific cell alterations with the prelipoid granule content. The latter, by variations in its staining reaction, manifests merely stages in the development of the disease process. Moreover, in a great number of instances differences between the histologic alterations of representative members of the several groups are so slight as to be indistinguishable. Comparison, when made between two such remote forms of the disease as the infantile (Tay-Sachs), on the one hand, and the juvenile (Spielmeyer-Vogt) type on the other, reveals even there that no sharp boundary line can be drawn between them. Thus, there is no escape from the conclusion that they constitute only variants of one and the same disease entity. In accepting this conclusion, one need not insist on the "total" ubiquity of cell alterations, for it is well demonstrated by the material herein reported, that even in the most typical instance of the infantile form of the disease, many cells may be found in a fair state of preservation. On the other hand, what is still more significant, is that

nerve cells in their wide distribution outside the central nervous system show the same type of disease process.

Further support for the unity of the disease is found in the observation that alterations characteristic of one group may be found in another in which such changes are said, as a rule, to be absent. Thus, Schob (31) and Rogalski (32) described cases, clinically identified as members of the juvenile group, in which they found widespread inflation of dendrites and axis cylinders, a feature usually absent or sparse in that form of the disease. On the other hand, the failure of a case to present all cardinal signs of the disease, need not place it outside the nosologic group. This is demonstrated by the three patients of Walter (33), all members of the same family, who presented the typical anatomic alterations, but clinically lacked the most common of the triad of symptoms—the impairment of vision. In this connection it is significant, as Walter had noted, that there is a great variability in the site of the lesion accountable for the impairment of vision, a dysfunction most common in this disease. Thus, in one instance he found blindness to be due to involvement of the retina, in another to affliction of the optic nerve, while in still another it was the result of disintegration of the visual cortex.

Great, perhaps somewhat too great, emphasis has been placed on the involvement of the cerebellum as a distinguishing feature of the late infantile form of this disease. Bielschowsky (34) called attention to the massive changes in the cerebellum in which he found the late infantile form of this disease. These observations, and those of Jansky (23), Sträussler (35), and Brodmann (36) brought this form closer to the juvenile variant of this disease. Westphal (37), however, reported a case of the infantile form of amaurotic family idiocy, in which he found a widespread sclerosis of the cerebellum, with the alterations being so advanced that he was led to designate it as a case of congenital cerebellar atrophy. In this connection, the case recently reported by Norman and Wood (18) as an example of a congenital form of amaurotic family idiocy, gains great significance. But, when the observations on the material assembled in this study are reviewed, it is noted that in no single instance of the twelve cases (including the one instance associated with hepato-splenomegaly) was the cerebellum free of changes which were of an intensity and distribution no less marked than those found in the cerebral hemispheres.

There is ample ground to assume that the clinical manifestations, as shown in the case of blindness, fluctuate in all other cardinal features of this disease depending upon the focal inroads made by the disease process on the nervous system. It is said that these fluctuations are more common in the late infantile form of the disease, because of the greater intensity and spread of changes in the white matter. The case of Brodmann (36) is quoted as an example. In his case the disease was ushered in during the third year of the patient's life by a slowly progressing mental depreciation, blindness, epileptiform seizures, ataxia, and paralysis. There was optic atrophy without the cherry red spot, and without *retinitis pigmentosa*. The anatomic findings consisted of atrophy of the brain, particularly of the cerebellum; the typical nerve cell alterations with

dendritic swelling, most marked in the cerebellum; extensive atrophy and rarefaction of the cerebral cortex, and vast disintegration of the subcortex with destruction of fibers and the mobilization of compound granular cells. Similar changes were present in the brain stem and in the spinal cord. Other cases of amaurotic family idiocy were described which were characterized by considerable disintegration of white matter; Savini (38) reported cases in which the subcortex was affected with the fiber tracts showing evidence of degeneration. Of interest is the opinion of Naville (39) that the demyelination is a form of arrested development affecting fibers in parts of the cerebral hemispheres phylogenetically and ontogenetically more recently developed. Extensive alterations in the white matter as found by Bielschowsky (24) in the late infantile form were noted by Globus (15) in several cases of the infantile variant of the disease.

This process of demyelination tempts one to speculate on the relationship between amaurotic family idiocy and another degenerative disease, described by Mertzbacher (40) as *aplasia axialis extracorticalis.* This malady is said to develop during the first months of life; it is rapidly progressive until the sixth year of life, after which its tempo is slowed. At its height the disease is characterized by nystagmus, slow and labored speech, difficulty in the execution of motor functions, disturbance of the succession and coordination of movement, ataxia, intention tremor, comovements, partial paralysis of trunk musculature, paralysis and spastic contractures of the lower extremities, increase in patellar reflexes, pathologic reflexes, and absent abdominal reflexes. Added to the latter are frequent manifestations of trophic disturbances of the bones, vasomotor disturbances in the lower extremities, and lowering of mentality. Here, however, the total absence of nerve cell alteration would make it difficult to admit this rare form of disease into the group of amaurotic family idiocy.

Not so, however, in the case of the Niemann-Pick type of hepato-splenomegaly associated with manifestations of amaurotic family idiocy. There, the alterations in the nervous system are almost indistinguishable from those found in amaurotic family idiocy. Brought to our attention first by Niemann (41), who in 1914 described it as an unknown morbid condition, it was Bielschowsky (42) and Bielschowsky and Pick (43), who by linking the Niemann-Pick splenomegaly with amaurotic family idiocy, advanced the understanding of the pathogenesis of the latter, a topic to be discussed elsewhere in this article. For the present it will suffice to say that Pick's interpretation of this morbid state as an expression of a disturbed lipoid metabolism productive of unusually large storage of lipoid material in the histiocytes of the various organs is accepted now also for the disease process affecting the cell components of the nervous system. There appears to be ample evidence that the alterations in the nervous system in cases of amaurotic family idiocy, when associated with hepato-splenomegaly, are, at least qualitatively, similar to those found in cases of the same disease unassociated with Niemann-Pick disease. There are, however, as pointed out by Hassin (44) some quantitative differences as shown by greater distortion and inflation of cells and their processes, and more massive liberation of neutral fats.

REMARKS ON THE PATHOGENESIS OF AMAUROTIC FAMILY IDIOCY

The early views held by Sachs and those held by Schaffer on the probable factors in the causation of this disease have already been reviewed in the introductory remarks. The concept of Sachs that the disease is an affliction of the nervous system, primary in origin and degenerative in character, still stands, provided that it is brought into harmony with the observations that have recently come to light. On the other hand, Schaffer's hypothesis that it is a heredo-degenerative disease restricted to neuroectodermal derivatives (nerve cells and glia) and transmitted through the hyaloplasm, does not fit into our present understanding of this disease and remains little more than an unproven hypothesis.

There are several well established facts in this disease: It is hereditary and familial in nature; it is non-inflammatory, and there is a strong probability that it is congenital in spite of its apparent abrupt onset in a hitherto apparently normally developing infant, child or adolescent. This is supported by the case recently reported by Norman and Wood (18) and probably by several cases of my own group (Cases 8 and 9). This observation leads to the thought that an individual affected by this disease may harbor in his brain and other parts of the nervous system many cells already altered by the disease and still retain enough normal cells to maintain somewhat satisfactory function of the nervous system. This is obvious from the fact that in a child who already manifests the disease, the nervous system may remain at work for some time though in a restricted and abnormal fashion.

The probability of the congenital origin of the disease is borne out by the fact that the brain is not a fully ripened organ at the end of the intra-uterine period of development. The histogenetic process continues for some time during the post-natal life of the individual. Thus, any interruption in the normal evolution of the cell growth and maturation may lead to stagnation, regression, and final disintegration of the affected cell elements. Such a course may be due, as pointed out by Edinger, to a shortage or depreciation of the construction material essential for the normal growth and existence of the cell.

There are those (Spielmeyer (26), and Bielschowsky (34)) who regard the disease as the result of disturbed metabolic function, a cause which is common to all variants of this disease. The metabolic disturbance resulting in the excessive intracellular deposits of lipoid substance and the secondary breakdown of the intracellular osmotic balance, is due, in the opinion of Marinesco (45), to the lack of a specific enzyme. There is also the view of Ostertag (46) who suggests the possibility that disturbance in the metabolic function of nerve cells has its origin in a trophic disturbance of the glial apparatus, the latter situation being provoked by some hormonal dysfunction.

The recent observations on cases of Niemann-Pick disease such as are associated with changes in the nervous system which duplicate those found in amaurotic family idiocy, have shed a great deal of light on the problem. Sachs (47) now accepts the views of Bielschowsky and others that the coexistence of

the generalized lipoid histiocytosis, particularly, in the liver, spleen, and lymph nodes with "similar accumulations of lipoid substance in the nerve and glia cells in amaurotic family idiocy," is not a coincidence but they are all an expression of a common underlying factor. It is a form of disturbed lipoid metabolism, which leads to an abnormal storing and distribution of this material, resulting in a malformation and disintegration of the affected cells. Thus, it may be said that the change in the brain in amaurotic family idiocy is but a part of a general disorder of the lipoid metabolism of the organism.

Significant as the new observations on the pathogenesis of the disease are, they nevertheless do not detract much from the earlier views of Sachs when his first impression was that the disease was a form of *abiotrophy* or *agenesis*. The subsequent views of Poynton, Parsons and Holmes (48) that the disturbance is in the inherent chemical constitution of the cells, come close to our present concept, but again do not obscure the original idea of Sachs. Now, if we admit that no sharp line can be drawn between the chemical constitution of the cell and its morphology, and that one is dependent upon the other, then it can be readily accepted that regressive morphologic changes may result from provision with defective constructive cell material, or from an inadequate utilization of satisfactory material. Hence, it can be said that cells poorly endowed with constructive material or with means to utilize satisfactory material may at some critical moment in their existence no longer be able to subsist and function properly. With their development interrupted or brought to a stop, regressive and disintegrating changes may conceivably ensue in a manner noted in amaurotic family idiocy. Thus, we come to an important statement made by Sachs (49) in 1905: "The author still firmly believes that amaurotic family idiocy is due to an arrest of development, and that this arrest of development is followed by degeneration. Accepting Gower's and Edinger's view of inherent or deficient capacity for normal development, we may argue, that children who are afflicted with amaurotic family idiocy, have a very limited capacity for normal development."

GENERAL CONSIDERATIONS

The observations recorded in the foregoing pages are based in part upon studies which I began a little over twenty years ago, and published somewhat later (15). In that communication a few new observations were added to what was already known in respect to the histologic character of the disease under consideration. It was shown that in its infantile form the disease does not spare the white matter nor does it affect the cerebellum only in the exceptional instance. In the course of twenty years a larger series of cases came under my observation, and thus a considerable quantity of material became available for further histologic analysis. This was carried out with particular regard for the significance of the deviations manifested by the several variants of this disease. It offered also the opportunity to make a few new disclosures as to the distribution of the disease process. Once again it became possible to emphasize the ubiquity of the pathologic process as it affects the components of the nervous system by demonstrating the

characteristic nerve cell alterations wherever such cells are encountered including abdominal and pelvic viscera. Less typical, but no less significant, are the alterations found in the posterior lobe of the pituitary, a structure of neuroectodermal derivation and embryologically a part of the nervous system.

All this favors strongly the view of Schaffer (50) that in amaurotic family idiocy the disease process is selectively restricted to neuroectodermal derivatives and hence it may be regarded as a germ layer (system) disease. Moreover, one is tempted to speculate on the probability that among the derivatives of the neuroectoderm, only those which participate actively in the functions of the nervous system are affected by the disease process under consideration. This observation finds support in the fact that the ependyma cells and the pineal body, both of which are neuroectodermal in origin, do not display the characteristic cell changes. Schaffer's concept is weakened by the concurrence of manifestations of amaurotic family idiocy with those of Niemann-Pick disease (spleno-hepatomegaly). It is rather difficult to harmonize the views of Schaffer with this phenomenon, and consequently with the newer concept on the pathogenesis of the disease process in both amaurotic family idiocy and the splenohepatomegaly of Niemann-Pick. To overcome this difficulty Schaffer (50) modified his concept by suggesting the probable involvement of both ectodermal and mesodermal germ layer derivations.

Without entering into a discussion of the chemical identity of the degeneration (lipoid) products in either amaurotic family idiocy or Niemann-Pick variant of the disease, it may be said that there is little doubt left now that the disease process is an expression of an endogenous metabolic disorder resulting in a deposition, or better, in the failure of assimilation, of lipoid material. Schaffer takes issue with those who support such views. He denies that the so-called prelipoid granules which crowd the affected nerve cells, are derivatives of lipoid material brought to the affected cells, and maintains that they are products of disintegration of neuroectodermal ingredients of the affected cells. Moreover, he emphasizes the absence of the mesodermal transport cells, the cells of Niemann-Pick disease in the infantile form of amaurotic family idiocy. He comes to the conclusion that in both instances an endogenous factor is responsible for the metabolic disturbances. In the case of Tay-Sachs disease, it is due to a congenital, constitutional and familial in nature, inherent weakness or "abiogenesis" of the ectoderm, while in Niemann-Pick disease, it is due, in addition, to a similar weakness inherent in the mesoderm. Indirectly, Schaffer accepts a disturbance in lipoid metabolism for the histologic manifestation of amaurotic family idiocy. In return, a concession may be made to him by recognizing that in the typical uncomplicated form of the disease, the disease process, restricted as it is to the neuroectodermal elements, is also all inclusive for those elements, affecting them in remotest parts of the organism, even in secluded parts where only a single cell may be encountered. Hence, it may then be accepted for the present that the disease has as its cause an endogenous factor, probably expressed in a great number of instances in an inherent weakness restricted to neuroectodermal derivatives. This weakness is expressed in the inability of the

affected tissue or tissues to assimilate the lipoid material essential for its normal and continued existence. This in turn leads to dysfunction and disintegration of the cell structure, the elaboration of products of dissolution, often reduced to the state of free fats. When the several so-called forms of the disease are considered in the light of the above considerations, then it becomes obvious that they constitute variants corresponding to stages in the intensity and spread of the disease process. It is not unlikely that the widespread disturbance in the lipoid metabolism noted in Niemann-Pick disease, in which the nervous system when involved shows most pronounced changes, is another example of the greater intensity of the disease process.

The assumption of an endogenous factor in the causation of this disease directed the attention of several observers, including Marburg (22) toward a probable hormonal disturbance as its source. However, it is found that no convincing proof has as yet been produced to implicate the glands of internal secretion in the provocation of the disease. My own material definitely excludes the parenchyma of such glands (excepting the posterior lobe of the pituitary) in participating in the disease process.

SUMMARY AND CONCLUSIONS

1. A brief historical review is given of amaurotic family idiocy with particular emphasis on the contributions of the discoverer of the disease.

2. Clinical histories briefly are reviewed and detailed anatomical observations are presented on twelve cases of the infantile form of amaurotic family idiocy (including one case in which the affliction of the nervous system was combined with Niemann-Pick disease), and of one case of the juvenile form of this disease.

3. The clinical and anatomical features of other variants (late infantile, adult, and congenital form) are described and their relationship to the entire disease entity is discussed.

4. New observations on the ubiquity of the disease process are recorded; they include the disclosure of isolated cell groups outside of the central nervous system exhibiting cell alterations characteristic of the disease.

5. Attention is called to advanced changes in the posterior lobe of the pituitary and the unusually large globoid granular bodies found there in large numbers.

6. Evidence is offered in support of the view that the several forms of the disease, including one which is associated with Niemann-Pick lipoid histiocytosis, belong to a single disease entity, characterized by a disturbance in lipoid metabolism.

7. It is pointed out that too great emphasis has been placed on focal variations in intensity of the pathologic process, as noted in the several variants of the disease.

8. A study of endocrine organs in several of the cases here reported fails to provide evidence in support of the view that their dysfunction is at the base of the disease process. The presence of nerve cell groups within the territorial domain of some glands of internal secretion (adrenal, posterior lobe of the pi-

tuitary body) is thought to be no more than an item in the ubiquitous disease process affecting nerve cells everywhere.

9. The conclusion is drawn that broadly speaking amaurotic family idiocy is a malformation, expressed mainly in the endowment of the affected cell with defective constructive material or in its (the cells) lack of capacity for assimilating the available material. Either of these difficulties is capable of causing regressive morphologic changes, resulting in dysfunction and finally in the total disintegration of the affected cells.

Somewhat belated, but well deserved, thanks are hereby extended to my wife, who a little over twenty years ago helped substantially in the preparation of an earlier communication on this topic, one which served as the springboard for further work and thought, as well as the nucleus for this paper.

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THE TWO WAYS OF ADJUSTMENT OF THE ORGANISM TO CEREBRAL DEFECTS

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Understanding of the behavior of patients and intelligent treatment is possible only if it is fully realized that the symptoms of a disease consist not only of the direct sequelae of the damage but also of reactions of the organism to the damage. Disease is not simply damage to one or another part of the organism. Although impairment of specific performances corresponds to the damage, the symptomatology cannot be ascribed to this impairment alone. In the acute state, a number of symptoms appear which are not the sequelae of the defect but which are due to the disorder which affects the whole organism as a further consequence of the damage. Some functions are lost when the organism encounters conditions which prove catastrophic as it is no longer able to cope adequately with the demands of "its" environment. It therefore exhibits a strong tendency to prevent the occurrence of these conditions. This can be effected either by a change in the environment, or by modification of the organization of the organism, or by both. If *restitution ad integrum* does not occur, i.e., an irreparable defect remains, the symptomatology displays phenomena expressed in functions or performances which are not directly affected by the injury but which result from changes in the whole organism as it endeavors to adjust itself to the environment in which it must live despite the remaining defects. The process of modification has a twofold effect: it may limit or completely prevent the occurrence of catastrophic reactions, thereby guaranteeing ordered behavior of the whole organism; it may make it possible for the organism to gain a new environment, adequate to its changed condition, and thus allow for the best possible utilization of the remaining capacities. These two effects represent merely two aspects of the same process, namely, the acquiring of a new ordered functioning which is requisite for the existence of the organism. Therefore, recovery always entails, if *restitution ad integrum* is impossible, a shrinkage of the *milieu* and the forfeiting of some performances. What happens in a given case depends upon the individuality of the patient and the severity of the defect. The latter is determined by the significance of the disturbed function for the "normal" life of the individual, and by the possibility presented by the surroundings of attaining a new *milieu* adequate to the changed capacities of the individual, i.e., by the opportunity which the surroundings present for the individual, in spite of its limited capacities, to live in a satisfactory way. From this point of view, significant for the well-being of the organism as a whole, there is an assortment of defects. If the organism has found a new adjustment, i.e., a new state of orderly existence, we may be sure a definite selection in this respect has taken place. Space does not permit a fuller discussion of this topic and the reader is referred to my book, The Organism (3). For the immediate

needs it is sufficient to point out the following: although a new order may be attained, the organism is still incapacitated in some respects; this incapacitation, however, is basic for the maintenance of the new state of order; it permits the utilization of the remaining capacities because only then are catastrophic conditions largely avoided in a given *milieu*.

With this point of view, the symptomatology of a given case becomes understandable. It calls, however, for a careful study of the new arrangement which insures ordered behavior in spite of a remaining defect. Therapeutic endeavors can follow no better course than that provided by nature. They can do no more than support the organism in its attempt to regain an ordered condition. The recognition of the significance of each symptom for the maintenance of order is essential to decide which symptoms are to be eliminated and which are to be left untouched, otherwise a condition of disorder may result. In respect to those symptoms which have proved to be indispensable for the adjustment of the individual as a whole, we can only help him to bear their disagreeable consequences.

This attitude toward therapy was never completely overlooked. However, it was neglected or emphasized in accordance with the degree of recognition of the holistic approach to medicine received in various periods. It is a tribute to Freud that he stressed the importance of this point of view for psychotherapy at a time when it was most neglected. Experience with patients with organic diseases as well as with functional disorders has induced me for many years to emphasize the significance of such an evaluation of symptoms (4). In this paper it is my intention to demonstrate the significance of this attitude for an understanding and correct treatment of organic disease. I shall present some case material to demonstrate particularly that the new ordered functioning may be acquired in two diametrically opposite ways. The organism either adjusts itself by yielding to the defect, i.e., resigns itself to the abnormality of some functions and to certain changes in the *milieu* as a consequence of the defective performances, or the organism faces the defect, and readjusts itself in such a way that the defect is kept in check.

Case 1. Mr. Q, a bookkeeper, 40 years old, suffered a skull injury on the left side near the ear. The wound never totally healed. Four years after the injury, he experienced pain behind the left ear, a burning sensation in the ear, temporary discharge of pus from the ear, attacks of headaches, and dizziness. When the discharge from the ear had ceased the symptoms disappeared until the next attack. The diagnosis at that time was serous meningitis due to chronic inflammation of the left ear. Fourteen years after the injury, the patient came under my observation. He complained of severe headaches in the left side of the head, particularly behind the left ear. During one attack he lost consciousness. He always felt somewhat dull.

Examination. Hearing was not essentially diminished. There were changes in the left middle ear due to the old injury. The vestibular test showed a hypersensitivity of the left labyrinth. He had a left peripheral facial weakness. The tongue deviated a little to the left. The left eye was in a position of slight convergence. On lateral gaze the left eye did not follow to the end-position; diplopia in this position indicated a left abducens paresis. The pupils were equal and round; their reactions were normal. There was no nystagmus. The visual fields were normal. The fundi were negative. The left conjunctival and corneal

reflexes were somewhat reduced. There was tenderness to pressure over the supraorbital point of the left trigeminal nerve and over the left occipital nerve behind the ear. There were no changes in reflexes, or motility.

When the patient lifted both arms to a horizontal position with eyes closed, the left arm did not go up as high as the right. When the patient's arms were raised passively to a horizontal position, his left arm drooped about 12 cm. and deviated a little outwardly, and then stopped, without the patient becoming aware of these changes. In the finger-to-nose test, the left arm deviated toward the left side, and there was past-pointing of the left arm towards the left side. There was no adiadochokinesis, and no astereognosis. There were no disturbances of sensation except those of localization of touch points on the skin of the left side of the body. When the patient used his right arm, he pointed beyond the touch point stimulated (5).

The diagnosis of this case was serous meningitis of the posterior cerebral fossa from which resulted abnormal excitability or damage of some cranial nerves (fifth, sixth, seventh, eighth and twelfth) and a damage to the function of the left cerebellum. Due to this last damage, there was a disturbance of the equilibrium with a tendency to deviate toward the left side in order to attain an abnormal "preferred" position of the head and body. In this position, with the body tilted to the left, the patient felt subjectively best and showed almost normal reactions in tests of various motor and sensory performances: e.g., pointing, localization of points on skin, etc. Both the subjective position and performances became worse if the patient was forced to hold his head or body perfectly erect. Under these conditions, he experienced a pull to the left side which disappeared immediately upon assuming a tilted position, i.e., his new "normal" position.

According to my theory of the function of the cerebellum (5), there is in lesions of this part of the brain an abnormally strong reaction to stimuli exciting the homolateral side of the body. There is an abnormal turning of the organism or of the stimulated part toward the source of stimulation; an abnormal "to-turning" tendency. The patient experiences this as a pull toward the affected side. The effect of a stimulus and likewise the size of the to-turning movement varies with the distance from the point of stimulation to the midline, i.e., the farther the stimulation is from the midline, the greater is the effect. Touching a point on the outer part of the chest is more effective than touching a point near the midline. Stimulation of the eye by light more laterally situated is more effective than by light situated nearer to the midline. The abnormal to-turning tendency causes the withdrawal of the affected side away from the midline of the body. Many patients graphically describe this feeling of abnormal drawing away. The visible effect is spontaneous falling, deviating, and past-pointing. The orientation of a man standing with eyes closed is determined by the stimuli acting on the labyrinths, the skin, the muscles, and other sense organs. The effect of the usual environmental stimuli is equally strong on both sides. Consequently, there is an equilibrium established between the equal withdrawing outward of each side, and therefore correct standing, walking, pointing, etc.

There is one peculiarity in the behavior of these patients which demands

special attention. The affected arm deviates only a certain distance away from the midline of the body, then deviation stops. When past-pointing is tested in this region, the patient no longer past-points. This is because the deviation is the result of two factors: first, the abnormal to-turning tendency, and second, another behavior-change which I have called the tendency to resume the "optimal behavior" (6). The position to which the arm or the head deviates corresponds to the position which usually prevails in the patient's postures and performances. The normal organism also has the tendency to prefer certain postures, movements; namely, those in which it is in the best adequate balance with the surroundings. This condition is subjectively the most agreeable, and its maintenance objectively requires the least energy. The organism, however, is also able to choose inconvenient attitudes and to maintain them when the situation demands. This is anatomically sustained by the innervation of the forebrain. Moreover, the normal person is capable of accomplishing this even without paying constant attention to posture, because the innervation of normals is supported by the coinnervation of the cerebellum. For example, the most convenient position in which to hold the extended arms is with palms downward. But the normal person is also able to hold his arms with palms upward or in even more difficult positions. In these inconvenient positions, the normal individual feels the tendency to go back to the more comfortable or optimum posture. However, he is able to maintain the inconvenient posture without paying constant attention to it and without continuous voluntary innervation. In contrast to this, the patient with a cerebellar lesion may not be able to bring his hands to such an inconvenient position at all, or if he can, he cannot maintain it without steadily paying attention to and constantly correcting the position. For example, unable to assume a demanded position with eyes closed, he brings his hand to a more convenient position rather than the position required. Or, if the patient with eyes open has brought his hand into the demanded position, his hand turns to the "best" position immediately upon closing his eyes. All these changes occur without the patient being aware of them.

It is quite well established that while the abnormal position of the head, arms, legs, etc. observed in patients with cerebellar or frontal lobe lesions (5, 10) are caused by the hyperexcitability to external stimuli, they are also symptoms of a new adaptation. The patient shows a preference for a particular position because he feels best and is able to act best in it.

The abnormal position represents an adjustment of the whole organism to the defect and a new ordered functioning. This is confirmed by the fact that under this condition most of the abnormalities previously observed disappear, or are substantially decreased, and that the organism is able to utilize more effectively its remaining capacities.

In this type of patient the best adjustment is achieved by the deviation of the body in the direction of the abnormal pull, i.e., toward the diseased side (the side of the lesion of the cerebellum). However, there are cases of cerebellar disease in which a deviation of the body takes place in the opposite direction,

i.e., towards the normal side. Poetzl has reported such observations and I have carefully studied this condition in several cases. I would like to refer to one of these cases here.

Spontaneous position with open eyes, deviation of head to right.

Passive elevation of head.

Going back of the head to the spontaneous position without the patient being aware of it.

Head tilted passively to left.

Going back of the head to the spontaneous position without the patient being aware of it.

Passive tilting to extreme right.

Going back of head to the spontaneous position without the patient being aware of it.

The above figures illustrate the tendency of the patient to obtain a definite "preferred" position in a case of left frontal lobe lesion.

Patient with lesion of the left frontal lobe. Shows tendency to fall to the right side, past-point etc., when his head is in an upright position. To compensate, the patient holds his head tilted to the right side (fig. 1). In this position (his new "preferred" position), he performs best and feels most comfortable. When his head is passively brought to any other position, it returns to the "preferred" position without the patient's being aware of it. Figures 2–5, 6–10, 11–12, which are pictures from a movie illustrate this phenomenon. In figure 2, the head is passively placed in an erect position, in figure 6, in a position somewhat to the left side, and in figure 11 too far to the right side. Note position to which head returns in figures 5, 10 and 12, is always the same.

Case 2. The patient suffered from a serous meningitis in the left ponto-cerebellar angle. He presented a paresis of the left sixth and eighth nerves and displayed disturbances of equilibrium. In walking and standing with eyes closed, he showed a tendency to fall to the left. Past-pointing to the left side of the left arm was also observed. Testing of the

labyrinths showed intense hyperexcitability of the left vestibular nerve. The patient felt a constant pull toward the left. Furthermore, his ability to estimate weights with the left arm was disturbed and there were disturbances of localization and space perception, which were of the same type as those found in cerebellar cases. He always held his head slightly tilted to the right. His body also deviated to the right. In this position, he felt subjectively best, was not dizzy, and showed improvement in the objective performances. The moment the patient would lift his head upright (or his head was raised passively) he felt dizzy, had headaches, and was in danger of falling to the left. Testing the previously mentioned performances under this condition showed an enormous increase of all the symptoms. It was clear that the position of the head tilted toward the right represented the condition in which the organism as a whole was in best order and represented the preferred position of this man. It may be considered an expression of compensation.

In both cases (cases 1 and 2) through the posture anomaly, specific performances improved, catastrophic conditions diminished, and a new order was established. The question now arises as to why these two patients, both suffering from a damage to the left cerebellum compensated in opposite ways: the first by deviation of the body toward the diseased side, the second toward the healthy side. Furthermore, why should best order of the whole organism result from opposite ways of compensation? We can state the problem in another way by saying: in the first case the organism found a new order by yielding to the tonus pull, while in the second case the organism checked the effect of the tonus pull by producing a pull in the opposite direction. In an attempt to explain these different behaviors, we must view the cases in the light of other existing differences. One outstanding difference is that in the second case, in which a new order was established by deviating toward the right (healthy) side, the tonus pull was very much stronger than in the first case. In the latter case, the patient merely showed a tendency to fall, but did not actually fall, even when his head was in an upright position. With his head tilted to the left (affected) side, good equilibrium was maintained. The stability of the second patient was affected to a much greater degree. He was always in actual danger of falling. He could walk, sit, or stand, only when his head was markedly deviated to the right. Falling resulted immediately upon straightening his head, or tilting it to the left. Under these conditions, he was easily thrown into great disorder and all his performances were very disturbed.

It may be said that in principle the disturbance is the same in both patients. It consists of a tonus pull to one side and an abnormal to-turning tendency to stimuli affecting this side. The difference is one of degree. The degree of disturbance was very much greater in the second patient. Hence the second patient was always in extreme danger of losing his equilibrium. In the first patient the abnormal pull can be eliminated and a new condition of order reached by tilting the body towards the side of the pull. Now equal stimuli produce equal affects on both sides. However, if the second patient were to follow the same course of adjustment, no condition of order would result. On the contrary, the patient would fall the more readily. The reason is that this patient, in order to eliminate the much stronger pull by yielding to it, would be obliged to assume an extremely oblique position, which in itself would represent

such an abnormality that no balance could be maintained. In this position, walking, standing or sitting would be impossible, and such an attempt at adjustment to the special defect would have no beneficial effect for the organism.

Certainly, the deviation to the left in the first patient is somewhat disturbing for his performances in general. However, it is in no way as disturbing for the whole organism as a continuous and permanent tendency to fall. Minor disturbances can be readily born by the organism. For the second patient compensation by deviation of the body toward the affected side (left) is impossible because of its influence upon the behavior of the whole organism. Therefore, the abnormal pull toward the left side has to be eliminated in another way, namely, by counterbalancing the abnormally strong pull by a pull in the opposite direction. By this procedure, equilibrium and a new order is obtained, which is confirmed by the fact that under this condition the patient feels subjectively best, and in all the performances mentioned, which were so greatly disturbed with the head erect, the patient shows almost normal behavior.

Thus we are led to the conclusion that the difference in compensation (i.e., tilting the body to the one side or the other) is due to the difference in the severity of the defect. The new order is always reached in a way which by itself is conducive to the best condition of the whole organism. This means that performances can be executed in the best possible manner, and that the subject feels most comfortable.

These differences in deviation may strike us as being different symptoms resulting from different lesions. However, it must be realized that symptoms in patients with the same disease may vary according to different modes of compensation. In view of this, it need not be concluded that the same symptom is necessarily indicative of the same underlying lesion.

I would like to illustrate the approach presented here with another example from a totally different performance field. It concerns the different behavior of patients with hemianopia and hemiamblyopia. It is a well known fact that patients with hemianopia (i.e., blindness in both eyes of corresponding parts of the visual field) in every day life seem to recognize objects within an area where according to perimetrical examination, stimulation is ineffective. Subjectively they are aware of a somewhat impaired vision. But it is by no means true that they see only one half of an object. Precise exploration shows that the patients are not limited to half a field of vision, in instances other than perimetrical examination, but that their field of vision is arranged around a center like in normals, and that likewise, the region of their clearest vision lies approximately at this center. It has been demonstrated (8) that a visual field of such formation is prerequisite for the most important visual functions, especially for the perception of objects. Apparently the hemianopic patient has found a new means of adaptation which allows for such perception. Inasmuch as the blind part of the retina is not sensitive to stimuli, it might be concluded that perception originating in the part of the outer world corresponding to the blind half of the retina, must have been registered on the other part, i.e., the intact half of the retina. Careful investigation actually shows this to be the case. When the

patient is presented with a series of figures on a blackboard, and asked to state which one he sees most distinctly, he does not designate, like a normal person, that figure which would register on an area corresponding to the macula, but one which lies a little further to the side. Apparently, that point in the outer world seems clearest to him which is reflected not on the border of the intact retina, where the old macula now lies, but on an area *within* the intact retina, i.e., a so-called pseudo-fovea has developed (2, 7). The latter could happen only if the eyes shifted their position from the normal position. Such a displacement can actually be observed. Normally, when looking at a series of objects in sequence, with the intention of seeing each one clearly, the eyes move in such a way that the objects in question are always focussed on the macula, in which position they always occupy the center of the visual field.

This state of affairs is attained in the patient by the displacement of the eyes. Thus the patient regains clear vision despite the defect of his visual apparatus. That this transformation is an expression of a tendency toward maintaining optimal performances is clearly shown by the fact that it occurs only when the calcarine cortex is completely destroyed—in other words, when this side of the calcarine is really unable to register impressions which can be used in the perception of objects.

In hemiamblyopia, where the damaged calcarine cortex is still capable of performing this function, even though to a reduced extent, where, in other words, a characteristically formed visual field still can be built in the usual way, the described transformation does not occur. Even though one-half of the objects produce a fainter impression, this apparently does not disturb perception essentially—not to such an extent that the displacement is demanded. As long as that is not the case, this transformation will not occur, because such transformation in itself entails disturbances of the total behavior. The displacement of the eye required in hemianopia, must limit the extent of the visually prehensible outer world. This may involve not only mere quantitative limitations, but also deficiencies of a qualitative nature: for instance, when a complete recognition of an object requires that the perception also includes a part of the object which lies farther to the side. In addition to this limitation of the visual sphere, by the displacement of the eye, there may be some restrictions of the total behavior of the patient. The organism bears all these impediments, if a good vision is otherwise impossible; but it "avoids" them, if adequate vision can still be maintained in some measure without eye shifting—as in hemiamblyopia. What is pertinent is not the best possible performance in one performance field, but the best possible performance of the organism as a whole.

Accurate analysis of the behavior of hemianopic and hemiamblyopic patients supports the view that the method of adaptation is determined by the demands of the whole organism, by its tendency to regain those performances which are most important for the well-being of the whole organism. The organism is transformed in such a way that this state is reached. For adjustment to a hemianopic defect, the organism proceeds, in principle, in the same way as in adjusting to disturbances of equilibrium in cerebellar lesions.

These two kinds of adjustment to an irreparable defect are not accidental occurrences in the two specific disturbances mentioned. Such adjustments are observable in all adaptations to defects and can be exemplified by the behavior of patients with disturbances of various other kinds (3).

These two kinds of adaptation to the defect do not represent adjustments of equal value. In the first kind, "yielding to the defect", the normal functioning of the organism, is, in principle, unchanged. In this respect, it is a more "natural" procedure, it occurs more automatically, demands less voluntary activity on the part of the individual, and therefore insures more security. In the second kind of adaptation, the normal form of functioning is changed. It represents a more volitional kind of behavior, leads more readily to fluctuation, and therefore involves less security and admits a greater possibility for catastrophic reactions. This kind of adaptation, however, allows the organism to function more normally in respect to specific performances, for example, vision is clearer in cases of hemianopsia with pseudo-fovea than in cases of hemiamblyopia. As we have stated earlier, the avoidance of catastrophic reactions is a principle endeavor of the damaged organism. Therefore, the old "normal" procedure will be maintained as long as it is at all possible to carry out in this way performances essential for the organism as a whole. Only when the first type of adaptation no longer serves this purpose, when it can no longer function except by producing an unbearable impairment of the whole organism, does the second type of adjustment appear. This illustrates again that only by considering the relationship of each symptom to the whole organism can the symptomatology in a certain defect of the nervous system become understandable.

In the consideration of a concrete case it must be borne in mind that the performance level which an organism endeavors to attain in spite of the defect, is also dependent upon the demands which arise from the surroundings in which the organism is forced to live. The way of adjustment may differ in patients with the same defect in accordance with the differing demands of the environment. In this respect, it is necessary to realize the fact that even for normals the same external *milieu* may exact different demands according to the attitude of the individual toward the world. This factor is especially true of sick people. Their attitude toward the world may be conditioned not only by some special disturbances, as in our cases a defect of vision or equilibrium, but also by other defects. A patient with an impairment of vision or equilibrium may also suffer from a hemiplegia or a mental deficiency. These latter disturbances may render useless an improvement of vision because under this condition such an improvement may be of little advantage. Hence, there is a different adjustment to the defect of vision or equilibrium, but still in accordance with the general rule, that the organism adjusts in a way which enables it to reach a new order adequate to its specific disturbances. Thus some patients with the same defect of vision or equilibrium may show symptoms concerning these functions different from the cases presented here where the damage was restricted to these functions alone.

The point of view presented in this paper is of value only if the total condition of the organism and its *milieu* is taken into careful consideration.

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PROGRESSIVE MUSCULAR DYSTROPHIES

Necropsy Studies in Four Cases

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In selecting a subject suitable for this volume, I have taken one that has ever been, and continues to be, of deep interest to Dr. Sachs and one in which he is now stimulating interest in some of the younger men to pursue studies whose aim is the reduction, or possibly the elimination, of the physically and mentally unfit. The most important direction, fundamentally perhaps, for the accomplishment of this, is a study of the basic factors underlying the principles of hereditary diseases or those diseases in which heredity obviously plays an important role—progressive muscular dystrophy is one of these.

My conviction is that the entire pathology of the dystrophies is not revealed in the changes observed in the muscle tissue alone and that more fundamental and etiologic activation for the local pathology should be sought. In this I find myself in accord with opinions expressed in an ever increasing literature which especially emphasizes the influence of the autonomic nervous system and the endocrines.

In seeking some lead in the direction of study of the problem, one must determine what structures are implicated in the cases, clinically, chemically and physiologically observed. One very important question is, whether the pathologic changes found in muscle are confined to those not physiologically under control of the autonomic nervous system. For this the results of a study of the "unstriped" or so-called involuntary muscle will have a direct bearing; furthermore, we must endeavor to learn more chemical and structural anatomic variations in other organs showing changes so often associated with primary myopathies.

Studies at the Montefiore Hospital and later in other institutions, strongly tend to confirm the opinion that the dystrophies in both typical and aberrant forms have far more complicated and extensive relationship to neurophysiologic processes, than the seeming simplicity of muscle abiotrophy.

Some twenty-five years ago, a publication of studies by Janney, Goodhart and Isaacson (1) were based upon observations in a group of nine cases of various types of progressive muscular dystrophy—one male and eight females. We had observed that certain clinical and pathological features seem to point to the conclusion that there was a definite association between the dystrophies and dysfunction of the endocrines. Realizing that the substantiation of such a view required evidence of metabolic nature, as well as clinical findings more or less constant in their presence, the metabolism and classical features of the cases were carefully studied. These cases were analyzed in order to eliminate some of the errors of interpretation that probably account for the variations recorded in the literature by many observers. Our cases were segregated and under con-

stant supervision in individual rooms and cared for twenty-four hours a day by nurses trained in metabolic study; a special diet kitchen was used and creatinine-creatin free articles of food kept strictly uniform during the period of experimentation. Briefly, we found a marked decrease in the preformed creatinine and the abnormal presence of creatin in the urine; low values of creatinine and normal creatin in the blood; hypoglycemia and delayed glucose utilization, as determined by an hourly blood-sugar curve. I need not go further into the details of the method of our investigation. Subsequent findings, some made years later, are in accord with our original observations. As to the implications of the creatin findings as they relate to muscle metabolism, one may say that while we are far from an adequate understanding of the production of creatin and creatinine in normal and abnormal metabolic processes, a definite relation between these substances and muscle pathology is reasonably established. The urinary creatinine appears to be a measure of muscle efficiency; this view is substantiated by the findings of lower excretion of creatinine in diseases in which muscular weakness is conspicuous, as in Graves' disease, myasthenia gravis, myotonia congenita and the dystrophies. The presence of creatin in the urine is pathologic. Our observations have demonstrated that the metabolism of carbohydrates is also defective in the dystrophies. Many other changes indicative of general endocrine disturbance were found in all of our cases; these include dryness and abnormal pigmentation of the skin, hypertrichosis, brittleness of the hair, trophic changes of the nails, unusual distribution of the subcutaneous fat and both hypertrophy and underdevelopment of the genitalia. In several of our cases there was retardation of growth, a symptom very commonly observed and reported in the dystrophies; that this is not due to lower nutrition of subjects of dystrophy is shown further by the peculiar osseous changes indicative of a true metabolic defect; the osseous changes found are characteristic.

I am inclined, with many authors, to consider a primary endocrine disturbance as the basis of the myopathies. The mechanism of this is not clear; experimentation has helped us but little; e. g., Markeloff injected various glandular substances into dogs and measured the muscular activity with the ergograph or kymograph upon electric stimulation. The thyroid, hypophysis, suprarenals and testicles were found to stimulate muscular functional activity; the remaining endocrine glands were inhibitory. There seems to be no means of determining which gland is involved. From the standpoint of therapy this is unfortunate; however, we must face the possibility of the primary myopathies being really caused by deficient function not of one gland alone but of various endocrine organs separately or coincidentally affected. This is in accord with the observation that symptoms which are known to represent dysfunction of one gland are often similar or even identical with manifestations of affection of another ductless gland. For example, defective growth, abnormal bone formation and adiposity may result from lesions of pituitary, thyroid or sex glands; accordingly, if these symptoms are connected with widely different organs, it is not improbable that much of the pathology of dystrophy may likewise represent a symptom-complex capable of causation by dysfunction of various ductless glands, individually or grouped.

As already suggested, involvement of the cardiac muscle is not as uncommon as heretofore maintained. Because of the implications of the autonomic nervous system and its direct association with the endocrine organs, it is important to determine whether or not the cardiac or unstriped muscle is a part of the muscular pathology in the primary myopathies.

One of the most complete and illuminating studies on the pathologic findings in heart muscle in progressive muscular dystrophy is that by Globus (2), who states, "While observing the clinical course of several cases of progressive muscular dystrophy, my attention was called to the manner in which patients who had remained in *status quo* for fairly long periods of time, would, without warning, suddenly develop in rapid succession hypostatic pneumonia, pulmonary edema, hydropericardium and hydrothorax, culminating in death. Cardiovascular disturbance seemed best to explain these phenomena and in two cases reported by Goodhart and Globus lesions were found in the heart muscle essentially of the same character as those found in the skeletal muscle." After an interesting analysis of the literature and a further contribution of a study of two new cases of cardiac muscle pathology in the dystrophies, Globus demonstrated that the presence of cardiac involvement is far more common than is indicated in the literature. His conclusions are as follows: 1) The heart muscle does not escape the myopathic process characteristic of progressive muscular dystrophy; 2) it shows changes of a milder degree than those found in the skeletal muscle; 3) a few cases have been reported in which definite myocardial changes were found but they have not always been looked upon as a part of a generalized process; 4) probably myocardial changes would be more frequently found in progressive muscular dystrophy if the heart were systematically studied in every case; 5) the involvement of the heart muscle plays an important role in the terminal course of the disease and is perhaps responsible for some of the conditions which lead to a rapid and fatal issue.

In the article referred to by Globus, in which he and myself reported our studies on the nature of muscular dystrophies with especial reference to the changes in cardiac muscle in two cases with necropsy, some observations were made which I take the liberty of recounting at this time. We observed that, in spite of the occasional publication of post-mortem findings in the central nervous system, certainly no constant nerve changes have been described and in most of the cases reported, there is reason to doubt the correctness of the diagnosis of the clinical picture. We felt that the primary myopathies of themselves present no anatomical changes in the peripheral or central nervous system; we felt that the dystrophies are essentially distinct from the degenerative muscular diseases in which the pathology lies in the anterior horn cells of the cord and the analogous cells of the medulla oblongata. We stated then that in the light of later researches disclosing the interrelationship between body chemistry, the endocrine glands and the autonomic nervous system, we should critically reconsider the then accepted interpretation of the primary myopathies with progressive muscular dystrophy as its classic type as abiotrophy in which muscle tissue alone is the element of defective organization.

A review of the publications of studies on the finer pathologic changes since Meryon, in 1853, described his findings in the dystrophies as a picture of fatty and granular disintergration of voluntary muscle fiber, to later observations and reports of muscle fiber hypertrophy, pseudo and true, reveals various interpretations as to the nature of the process; even observations on the finer pathology have not been uniform. For example, most writers on the subject speak of true hypertrophy as sometimes observed. This is erroneous; there is no true hypertrophy in muscle fiber in the dystrophies. True hypertrophy, that is, physiologic enlargement of the muscle, means increase in sarcoplasm; hypertrophy as a physiologic process, after prolonged stimulation, does not show the splitting and loss of angular contour of the fibers with connective tissue proliferation and characteristic arrangement of nuclei in the cell, as one sees in dystrophy. The process is of the nature of a swelling and a part only of the general pathologic picture within the muscle. In the dystrophies, we rarely ever see true fatty degeneration; we find actual adipose deposits.

In studying the pathology of skeletal muscle we have failed to recognize the fact that striated muscles are not merely elements for contraction, serving the sole purpose of motility, but rather as structures possessed also of functions of equal importance similar to those of the organs of internal secretion. This was emphasized by Goodhart and Globus (3) in their studies on The Dystrophies. Muscle tissue in its process of physiologic activity elaborates a highly organized protein and is constantly building up glycogen from glucose and the latter is again broken up into simple sugars. McCrudden suggested that the myasthenia of the myopathies and the asthenia, seen in other conditions, in which we have hypoglycemia (Addison's disease, dyspituitarism, adrenalectomy, thyroidectomy, parathyroidectomy, phosphorus poisoning, etc.) are due to the reduced content of blood sugar. Great importance is placed upon disturbance of metabolism as associated with the primary myopathies. The production of creatin and creatinine and the elimination of sarcolactic acid and of carbon dioxide, all indicate that muscle is really a parenchymatous organ capable of function similar to that of the known glands of internal secretion. It is indeed probable that the primary myopathies, including Oppenheim's myotonia and amyotonia atrophica and the classical forms of dystrophies, have endocrine dysfunction as a direct or indirect etiologic influence. These conditions of disease, as revealed by careful study, associate them with disturbance of the organism involving metabolic processes and the osseous, trophic and glandular systems, with manifestations identical with those seen in polyglandular affections. As heretofore suggested, the body chemistry changes found in the dystrophies are of the same nature as seen in myxedema, Addison's disease, hypopituitarism, experimental thyroidectomy, etc. In four cases, which I shall report in this article, changes were observed tending to confirm involvement of the autonomic nervous system in the dystrophies. An excellent clinico-pathologic study of an entity identified with the progressive muscular dystrophies—dystrophia myotonica—was made by Keschner and Davison (4); they showed the pathology in the central nervous system consisted of changes in the ganglion cells of the lateral cells of the para-

ventricular and supraoptic nuclei. They suggest that possibly the neural lesions may be retrograde degenerations. They feel that the disease is one of a primary involvement of muscles—what they speak of as a true myopathy.

As previously stated, another problem of great interest relates to pathogenesis and heredity. It is a question how far the Mendelian laws apply in the problems of heredity relating to the dystrophies. The literature is replete with argument and divergent opinion. In a recently delivered paper on the Laurence-Moon-Biedl syndrome, I discussed the mechanism of the transmission of the elements of the syndrome as they seem to be transmitted through ancestral defects. In the opinion of students of the problem that particular group of manifestations (as seen in Laurence-Moon-Biedl syndrome) appears to be inherited as an autosomal recessive. However, as stated therein, mutation of a single gene could hardly be the cause of skeletal defect and retinal changes, with mental deficiency, obesity and hypogenitalism. It would seem that, in this syndrome, the polydactyly and other skeletal defects would rather be due to an abnormal division of the primitive mesenchyma or through some other mesodermal defect in development; the other elements of the syndrome must be the result of abnormality in the development of the retina and the diencephalon, both of which are of epiblastic origin (Ornsteen). Up to date there is really very little known and there has been much theorizing as to the mechanism of genesis in the transmission of hereditary disease. Polacheck (5) calls attention to the fact that the literature in America and abroad indicates acceptance of the belief that in some families progressive muscular dystrophy is a sex-linked Mendelian recessive trait and that the disease appears only in the female descendants of the non-afflicted female characters and in this respect has the same hereditary mechanism as hemophilia. Polacheck gives a geneologic record of a family in which ten males through generations suffered from pseudo-hypertrophy. The author refers to an article by Kostakow (6). The author records a family tree of three generations in which, out of forty-seven members living, fifteen of twenty male members were afflicted and twenty-seven females escaped. Family histories showing the same form of hereditary mechanism were recorded by Boshell.

A comprehensive study was made by Milhorat (7); of seventy-seven families analyzed, a total of one hundred and twenty members were afflicted. Observation of eighty-five of these patients, over a period of several years, showed the following: 53 per cent of the one hundred and twenty patients gave a history of at least one other member afflicted with the disease, and of the eighty-five patients who were examined, 34 per cent gave a definite familial history. The author found the sex ratio to be three males to one female. Twenty-six males inherited the disease by a simple sex-linked recessive factor. In seven males and seven females transmission was by a dominant hereditary factor. The exact mechanism of the hereditary in fifty-seven males and twenty-three females, though not determined, was of a recessive type. The author states that the sex chromosome carrying the dystrophy factor was probably transmitted by the females of the family for a number of generations without transmission to a male other than the patient and his siblings. The author also states, "another

possible type of hereditary transmission in one of multiple recessive factors in which the number of factors necessary to induce the condition is smaller in males than in females. A similar influence of sex on the number of hereditary factors required for certain characteristics has been demonstrated in many species of animals." We are still far from knowing the salient features underlying heredity in the dystrophies. Herein lies a vast *terra incognita*, most inviting for extensive investigation in this and other transmitted defects appearing in successive generations in entire or fragmental signs and symptoms.

The following is a study of four cases of progressive muscular dystrophy as analyzed from material available at Montefiore Hospital.[1] The deductions are only suggestive of involvement of the autonomic nervous system, as shown by changes in the parasympathetic cells in the cord.

CASE REPORTS

Case 1. History. B. N., a white man, 36 years of age on admission (November 17, 1911); 61 years of age at death. He experienced gradually increasing weakness in the right arm, two months later in the left arm and in both legs. The weakness gradually increased until the patient became bedridden. There were no sphincteric or sensory disturbances.

Examination. The patient was a well developed and well nourished man who, on general physical examination, showed nothing of note except an undescended left testicle. Neurological examination revealed a marked lordosis of the spine; gait was slow and wobbling and patient was unable to walk more than a few steps without assistance. He was unable to rise from the prone position. There was marked weakness of the muscles of all four extremities, trunk and neck; double equinovarus position of feet; marked wasting of the proximal muscles of the upper arms with pseudo-hypertrophy of the musculature in the lower limbs; dystrophic facies; deep reflexes were diminished throughout, except for normal ankle jerks; superficial reflexes were present; no pathologic reflexes; no sensory disturbances. The patient's head was dome-shaped (Turmschaedel).

Laboratory data. Repeated electrocardiograms (1935): Sinus tachycardia; left axis deviation; intraventricular conduction disturbance. X-ray examinations: Lungs (1934), infiltrations in the left lower lobe. Skull (1927), suggestive of increased intracranial pressure. Creatin studies not made.

Course. In 1917, the blood pressure was noted to be 180 systolic and 120 diastolic. From 1920 to 1925 he had occasional bouts of severe epigastric pain associated with leucocytosis and mild febrile reactions. These were believed to be due to possible cholelithiasis but cleared up on palliative treatment.

Neurological check-up in 1931 showed marked progression of the generalized weakness with intense atrophy of the proximal muscles of the upper and lower extremities and shoulder girdle with relative sparing of the distal muscles. The patient was completely helpless. No deep reflexes were elicited. Electrical reactions showed marked quantitative changes. Various forms of therapy, such as thyroid, gelatin, ephedrine and glycocol were tried, at various times, with no success. In 1932 sugar was discovered in the urine although the blood sugar was never markedly elevated. The patient was put on insulin thereafter and his diabetes was easily controlled.

In March 1935, the patient suddenly developed acute congestive failure which was believed to be on the basis of an acute coronary occlusion. In April 1935, the patient developed a sudden transient left flaccid hemiplegia during which the head and eyes were deviated to the right; the face was pulled to the right; the tongue deviated to the left; paralysis of left lateral gaze; bilateral Babinski and Hoffman signs; forced grasping on the right, and pseudo-athetoid movements on the right. The attack cleared up after one hour. The blood pressure during the attack was 230 systolic and 110 diastolic. The diagnoses considered were cerebral thrombosis, possibly cerebral embolization from mural thrombus in the left ventricle or angiospasm related to hypertensive vascular disease. In August 1935, the patient developed signs of another coronary accident. Fundus examination in November 1935 showed high myopia with no other abnormalities. On March 5, 1936, after several months of bed rest, the patient was allowed up in a chair from 3:00 to 3:30 P.M. At 4:15 P.M. he suddenly developed signs of left ventricular failure and, despite supportive treatment, he expired at 4:50 P.M.

[1] For aid in the interpretation of the pathology, I am indebted to Dr. Otto Marburg.

Clinical diagnosis. Progressive muscular dystrophy. Arteriosclerotic and hypertensive heart disease. Diabetes mellitus (mild). Generalized and cerebral arteriosclerosis.

Necropsy findings. Gross. Progressive muscular dystrophy. Cardiac hypertrophy. Generalized arteriosclerosis, including aortic and mitral valves and aorta with marked endarteritis of the abdominal aorta; arteriosclerosis of coronary arteries with narrowing (marked); old occlusions of anterior descending and circumflex branches of left coronary;

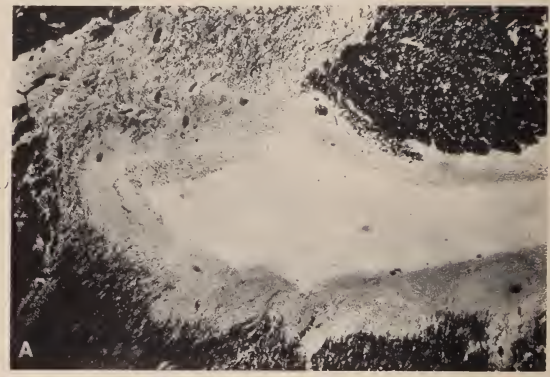

FIG. 1A. Syringomyelia. Stratum intermedium destroyed by syrinx (Weigert stain)

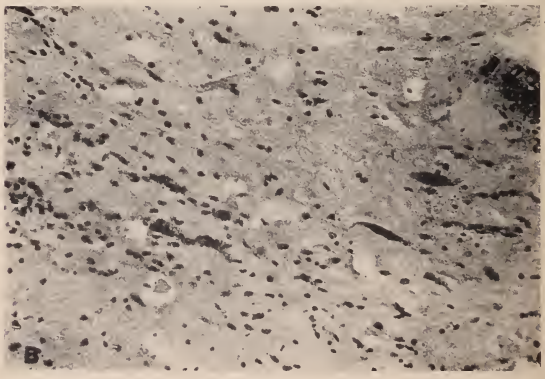

FIG. 1B. Dorsal cord, stratum intermedium, degenerated cells (Nissl stain)

old healed infarcts of anterior and posterior walls of left ventricle; chronic cholecystitis with cholelithiasis; arteriolosclerotic vessels of the kidneys. Edema of lower extremities; fibrosis and atrophy of testes; carcinoid tumor of ileum.

Microscopic examination. Suprarenals: gross-together about 10 grams in weight. They appear smaller than average for the weight of the patient. A section shows golden yellow cortex distinct from grayish brown medulla. Microscopically the cortex is rich in lipoid. Abundant medulla in parts.

Pancreas: A decreased number of islet cells. Area of interstitial fibrosis with some lymphocytic and plasma cell infiltrations.

Thyroid: One area shows calcification.

Pituitary: Congested capillaries with edema and fibrous thickening of intersinusoidal tissue of anterior lobe. Basophilic invasion of posterior lobe; overlying dura contains several hemorrhages and few psammomata.

Pineal: No pineal tissue.

Testes: Fibrosis and atrophy of tubules, quite marked in areas. Increase in number of interstitial cells of Leydig.

Muscle: Gastrocnemius: vacuolization and degeneration of muscle fibers with loss of striations. Extensive replacement by fatty tissue; increased number of sarcolemma nuclei with giant cell formation.

Temporalis muscle showed similar changes but much less marked and calcification of muscle. Other muscles show the same changes. The muscles of the lower extremities were nearly completely replaced by fat. Those of the upper extremities showed an increase in volume with loss of longitudinal and transverse striations; in these muscles fat was found only between the fibers; some fibers were replaced by connective tissue.

Other than an area of softening in the region of the caudate nucleus and the internal capsule and another area in the occipital lobe, there were only arteriosclerotic changes in the brain.

A syringomyelic picture in the lower cervical and the upper dorsal segments is clearly defined. The syringomyelia is, in part, hydromyelia, in part gliosis destroying the ventral third of Goll's and Burdach's funiculus and the tissue surrounding the central canal. The anterior horn cells in the region of the syringomyelic process are normal. Nearly all the cells around the central canal and dorsally at the basis of the posterior horn are entirely destroyed or profoundly degenerated; some of the cells in the lateral horn are likewise affected. Clarke's vesicular column has remained intact. The anterior horn cells in the third segment are severely degenerated. As to the peripheral nerve changes, the sciatic shows no real degeneration but some myelin discoloration; stained with osmic acid the nerve appears as though "covered with dust", but there is no reaction in the surrounding tissue; with Weigert's stain, the defects appear at the end of the nerve. Muscles: The picture is that of "dystrophic" muscles. There is swelling of some bundles, lack of transverse striations and longitudinally split fibers. There is ample fat between the bundles.

Surprising in this case is the fact that in the region of the syringomyelia, the anterior horn cells are almost normal and only the cells around the central canal are destroyed, whereas, in the lumbar intumescence the anterior horn cells are severely degenerated as are also those around the central canal. This does not anatomically correspond to changes in the muscles which are of the pathologic nature of dystrophy.

The involvement of the parasympathetic centers throughout the spinal cord is impressive. The lateral horn cells are practically normal. The changes in the peripheral nerves are too slight to be evaluated (figs. 1A and 1B).

Case 2. History. G. B., a white girl, was 14 years old on admission (October 23, 1921). The history was that of gradual onset of weakness in the legs since the age of five years and progression of weakness to complete paralysis upon admission. The patient began to walk at the age of 18 months and appeared normal during early childhood. A brother suffers from the same illness for the past two years.

Examination. She had the Froehlich type of body structure with marked adipositas, small ears, tapering fingers and thick dry skin. There was inability to raise the upper extremities, atrophy and complete loss of power of the muscles of the shoulder and pelvic girdles, hypertrophy of the calf muscles. The lower extremities were fixed in "frog fashion", flexed and externally rotated. There was areflexia except for active ankle jerks. The abdominal reflexes were present; there were no pathologic reflexes and no sensory changes. The cranial nerves were not involved.

Laboratory data. All tests were negative.

Course. During the patient's thirteen year stay in the hospital, there was continuous decrease in power of the muscles. She was given large doses of gelatin during 1932 with no change in her condition. She developed bronchopneumonia and died within two days on February 20, 1934.

Clinical diagnosis. Progressive muscular dystrophy. Terminal bronchopneumonia. Pseudohypertrophic muscular dystrophy.

Necropsy findings. Gross. Hyalinization and fatty infiltration of skeletal musculature. Bronchopneumonia, bilateral. Fatty infiltration of heart; cloudy swelling of heart muscle liver and kidneys; acute splenic hyperplasia; obesity; scoliosis right dorsal.

Microscopic examination. Liver: Passive congestion with marked fat metamorphosis of liver cells. In many cells the cytoplasm is entirely replaced by fat.

Suprarenals: Cells of cortex are devoid of visible lipoid; the medulla is infiltrated with lymphocytes.

Pancreas: Shows no changes.

Pineal and Pituitary: Show no changes.

Uterus: Atrophy of mucosa. Ovary: One corpus albicans, two graafian follicles without ova.

Muscle: Diaphragmatic and the psoas muscles show loss of striation; the fibers have undergone both hyalinization and replacement and separation by fat cells.

Spinal cord: Sections only from two levels of the upper cord are available; one from the medulla oblongata shows the following: The large anterior horn cells present essentially normal structure though with slight pyknotic changes. The small cells around the central canal as well as in the cornu lateral are shrunken with corkscrew-like dendrites. Similar changes are found in the small cells of the posterior horn. In Weigert preparations there are no signs of damage. Glia reaction: around some degenerated cells there are clusters of glia cells(neuronophagia). The meninges are thicker than normal and show slight signs of inflammatory irritation.

The lack of sections for an accurate examination of the spinal cord does not allow an evaluation of the above findings (fig. 2).

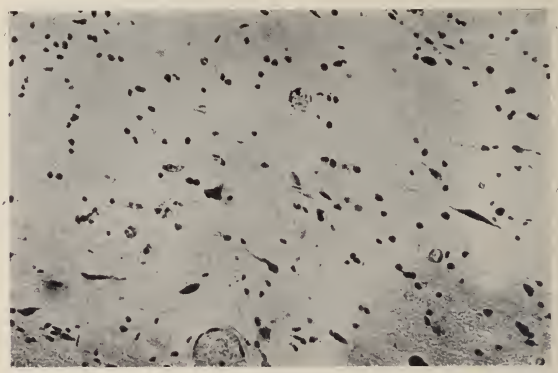

FIG. 2. Stratum intermedium: severe degeneration of the cells (Nissl stain)

Case 3. History. L. S., a white man, 44 years old on admission (April 26, 1915), died at the age of 59 years. The fatal illness began approximately at the age of 30, at which time he noticed a weakness of the lower extremities which finally invaded the upper extremities. Two brothers suffered from the same affliction.

Examination. The patient was an emaciated, chair-ridden individual. Weakness on lateral and upward eye-gaze was present. The tongue was large and fissured. Muscular wasting was diffuse and especially in the shoulder girdle and upper extremeties. The calf and deltoid muscles were large but soft and flabby. The muscles of mastication and sternomastoid muscles were involved but to a lesser degree. Trophic disturbances of the fingernails and extremities were observed. The deep reflexes were much diminished or entirely absent; the superficial reflexes were present and there were no pathologic reflexes. There were no cardiac symptoms and the blood pressure was 120 systolic and 80 diastolic.

Laboratory data. All tests were essentially negative.

Course. The atrophy slowly progressed; contractures of the limbs followed and secondary arthritic processes appeared. There was a questionable myotonic reaction in the voluntary hand grasp of the right extremity. There was the usual quantitative reduction to electrical stimulation of the muscles involved.

The difficulty that presented itself in this case was one of classification. In view of the late age of onset, the presence of coldness and cyanosis of the limbs, the peculiar onset and distribution of wasting, dystrophia myotonica (*sine myotonia*) was considered as a diagnosis.

In the terminal few weeks of his illness, the patient had been losing weight gradually and he became more increasingly weak and apathetic. Examination showed dullness and râles

at both pulmonary apices; breathing was harsh and bronchial in character over the left upper. The patient died of cardiac failure, December 8, 1929.

Clinical diagnosis. Progressive muscular dystrophy. Chronic pulmonary tuberculosis.

Necropsy findings: Gross. Chronic pulmonary tuberculosis. Cholelithiasis. Nephrolithiasis. Calculi in right ureter and bladder. Arteriosclerosis, kidneys. Chronic passive congestion, viscera. Coronary sclerosis. Myocardial infarction. Terminal bronchopneumonia.

Microscopic examination. Liver: Peripheries of the lobules show some fatty deposition whereas the centers are slightly congested. Many of the nuclei are somewhat vacuolated. Periportal areas in a few places are infiltrated with small round cells.

Testes: Spermatogenesis active. There is a very slight intertubular fibrosis and a few of the tubules are themselves fibrosed. There is a large cyst lined with low columnar epithelium which is filled with blue staining structureless material.

Epididymis: There is a slight increase in the stroma and corpora amylacea are numerous.

Suprarenals: Cortex contains a moderate amount of lipoid.

Thyroid: There are a few nodules in which the acini are variable in size but on the whole the architecture is fairly regular.

Pituitary: Oxyphilic cells are relatively few in number. Some of the acini are markedly enlarged.

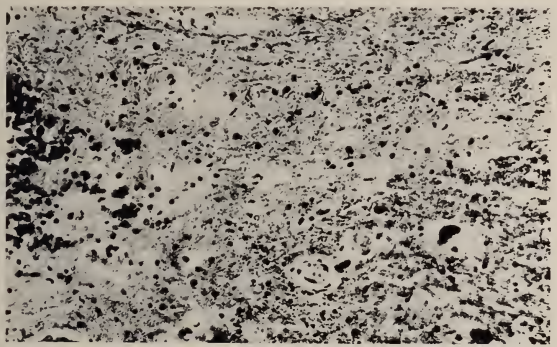

FIG. 3. Cells almost completely disappeared, detritus (Weigert-Fuchsin stain)

Parathyroids: There is a cyst filled with blue staining material. Oxyphilic cells are not observed.

Pineal: There are large cyst-like areas filled with very pale staining material. There is considerable calcification. The cysts have no demonstrable lining.

Voluntary muscles: From flexors of the legs and extensors of forearm normal muscular tissue is entirely replaced by strands of fibrous tissue between which is a large amount of fat. A few round cells are seen in the vicinity of blood vessels which are fairly numerous. They have not undergone any obliterative process.

The only available slides of the spinal cord are from the dorsal and lumbar levels. The cord as a whole is exceedingly small. The anterior horn cells are pyknotic and shrunken with corkscrew-like dendrites. The Nissl structure is well preserved. The cells of the lateral horn are normal at the upper dorsal level but the cells medial to them, around the central canal, are shrunken and present corkscrew-like dendrites; some are atrophic. Slides just below this level: The cells in the lateral horn are very severely degenerated, but in close vicinity of these sections, the lateral horn cells are normal again; the only severe damage is confined to the cells around the central canal. The anterior horn cells in the lumbar intumescence are normal but the cells near the central canal, dorsally at the basis of the posterior horn, are degenerated.

The changes in this cord are of a senile type with pyknosis in the dorsal parts. There is marked damage of the small cells around the central canal and in the region of the lumbar parasympathetic nucleus. Only one of the examined levels also shows a very severe degeneration in the lateral horn (fig. 3).

Case 4[2]. *History.* F. H., a boy, 10 years old, was admitted on September 2, 1936, with a flexion contracture of the left hip, knee and ankle, on the basis of a progressive muscular dystrophy. History, as given by the mother: The child showed progressive weakness of the lower extremities at the age of five; when he reached seven, he was unable to walk about because of weakness of the legs. The patient was admitted to the hospital for release of the flexion contracture of the left hip; this was performed on September 4, 1936. Seventy-two hours following operation the child died of respiratory paralysis.

On post-mortem examination the most outstanding feature was the presenee of fat in freshly sectioned lung tissue. The cause of death apparently was due to fat embolization.

Clinical diagnosis. Progressive muscular dystrophy. Flexion contracture of left hip, knee and ankle. Fat embolization with pulmonary edema.

Necropsy findings. Gross. Generalized muscular dystrophy. Pulmonary edema. Slight paralytic ileus. Recent postoperative hemorrhage into the left psoas-iliacus muscle, left hip joint. Anomaly of heart and lung (bifid aortic cusp, bilobed right lung). Osteoporosis. Coxa valga left. Mesenteric lymphadenitis.

Microscopic examination. Slight thymic hyperplasia. Brain and spinal cord: No outstanding pathologic changes except for some breakdown of myelin fibers in the dorsal spinal cerebellar tracts, less in the posterior column (status spongiosus). Slight diminution of the anterior horn cells with some sclerotic cells in the upper lumbar region is found.

Only a few slides from the lower part of the dorsal cord are available. The anterior horn cells are shrunken with corkscrew-like dendrites, but many of them are absolutely intact. The lateral horn cells are almost intact. The small cells in the middle zone ventrally and dorsally, are changed; pale, without structure, some are shrunken.

These few slides enable one only to record changes in the small cells of the pars intermedia.

DISCUSSION

The findings in the foregoing cases, as in most of those reported by other observers, are not uniform. This is true particularly in regard to the influence of the hormonal glands. The adrenals, in Cases 1 and 2, show some changes as do the pituitary in Cases 1 and 3; while in Case 1, the basophilic elements are increased; in Case 3, there is a decrease of the oxyphilic elements. The changes in the pineal body need not be regarded as significant, since such changes are not uncommonly found in older subjects. Similarly the fibrosis of the testes in Cases 1 and 3 may also be explained by the age of the patients—61 and 59 years old, respectively. The slight alterations in the pancreas in Case 1 and the cystic parathyroid in Case 3, need only be mentioned. Perhaps of greater significance is the thymic hyperplasia in Case 4, when considered in the light of its implication in other muscular affections; for example, myasthenia. It may be that the changes reported in the hormonal gland are of etiologic significance for muscular dystrophies; the cases here reported are not in themselves, by any means, conclusive. More important are the changes noted in the anterior horn cells, as found in Case 4, for example. Most striking is the fact, as in Case 1 with hydromyelia, that the anterior horn cells have remained intact in spite of the long duration of the disease. In this case the cells around the central canal (dorsomedial group of the ventral horn; intermediate cells, except for the cells of the lateral horn; cells at the base of the posterior horn) are severely damaged. All types of degeneration are seen but the chronic type prevails. This is the only common finding in all four cases and it is of some significance since the examination of the hypothalamic region and medulla have not revealed corresponding changes. These damaged groups of cells are connected with the vegetative part of muscular innervation; the cells of the lateral horn, almost intact in the

[2] From the Hospital for Joint Diseases.

reported cases are associated with sympathetic function. It cannot be decided however, whether the changes of the ganglion cells stand as an activating influence of the muscular affection or are the consequence thereof.

The investigations of other writers, particularly of Ken Kuré and his coworkers, emphasize the importance of the degeneration of these cells for the development of muscular dystrophy. The same observation was made in a carefully studied case by Gil (8). In the critical review of the literature by Romero, there are many other cases with similar findings. Thus one is justified in emphasizing this observation in our endeavor to learn more of the relation of the dystrophies to other structures.

SUMMARY

1. In four cases of muscular dystrophy the examination of the glands of internal secretion revealed some changes but not sufficient, however, to warrant the conclusion that there is a causal relationship between such changes and progressive muscular dystrophy.

2. Changes in the vegetative groups of the spinal cord were found in all of the cases; they appear to bear some definite relation to muscular dystrophy.

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SYRINGOMYELIA

Clinical Report of Ten Cases, Illustrating Spinal, Bulbar, and Congenital Types of the Disease, with Anatomic Confirmation in Three Instances[1]

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This study is based on an analysis of ten cases observed on the neurological wards of The Mount Sinai Hospital and the Montefiore Hospital for Chronic Diseases. They represent various types and all stages of the disease; particular attention is directed to pain which is not usually described as one of the more common symptoms. The clinical manifestations presented in a classical case of the cervical type, the most frequent type encountered, serves as an excellent example. In addition, there may be an immense variety of symptoms in any given case depending on the location and extent of the pathologic process in the spinal cord. These manifestations may be grouped as follows: 1) Motor disturbances; 2) sensory disturbances; 3) trophic and vasomotor disturbances.

1. Motor disturbances: Most frequently these begin with atrophic changes in the small muscles of the hand, and less frequently in other segments of the upper extremity or the muscles of the shoulder girdle. Where the small muscles of the hand become involved, the interosseous spaces become depressed; there is wasting of the thenar and the hypothenar eminences as the atrophy progresses and the hand assumes a claw-like attitude. The power in the hand gradually diminishes and the patient notices awkwardness in its use; buttoning of clothing, writing and other finer movements become difficult. Fibrillary tremors are apt to appear in the muscles undergoing atrophy. The electrical responses show deviations from the normal. If both sides become involved, the process usually advances more on one side. The muscles of the forearm, arm and shoulder girdle may progressively become involved. The deep reflexes at first are usually diminished or may even be absent, but where the pathologic process includes the pyramidal tracts, the deep reflexes and the tone in the muscles are increased.

2. Sensory disturbances: Combined with this slowly progressive atrophy and paralysis, there appears a form of sensory disturbance which is peculiar in its character and in its manner of extension. Perception of painful stimuli and those of heat and cold are disturbed. Slight disturbance to complete loss may be found in a given case. Only the response to either heat or cold may be disturbed. Extreme temperatures may alone be mistaken, the moderate grades of heat and cold may be correctly interpreted. All other forms of stimulation, touch, pressure, vibration, muscle and joint sensability are usually correctly perceived. This sensory dissociation may extend over one or both arms, and involve the

[1] This material was studied on the Neurological Services of The Mount Sinai Hospital and the Montefiore Hospital for Chronic Diseases, at the time they were under the leadership of Dr. Bernard Sachs.

neck, trunk, and lower extremities. The distribution of this disturbance is usually segmental and not confined to the area of distribution of a single nerve. As a result of these sensory disturbances, patients frequently receive burns about the hands, arms, and trunk. These burns are painless and are only recognized when the parts become blistered. Preceeding these sensory changes, the patients may suffer from intense burning paresthesias, or a feeling of coldness in the hands and arms. Girdle sensation may often be present. Subjective pain is not an infrequent symptom.

3. Trophic and vasomotor disturbances: These form the third group of symptoms in a classical picture of this disease. The skin of the hands is sometimes glossy and livid. Dermatoses of various forms may occur. Infection and ulceration tend to spread and may involve the subcutaneous tissues. Healing is protracted and sometimes impossible. Painless witlows occur which may lead to necrosis of the terminal phalanges with resulting mutilation of the fingers. The nails are greatly thickened, striated, brittle and, sometimes, they tend to drop off.

The long bones may undergo trophic changes in the form of rarefaction; spontaneous fractures occur infrequently. These fractures are usually painless and occur most frequently in the radius and ulnar. Scoliosis and kyphoscoliosis of the vertebral column is present in many of the cases. Spontaneous dislocations and painless destruction of the joints may occur. The joints of the upper extremities are most frequently affected. Unilateral hyperhidrosis occurs in many cases.

Owing to the frequent involvement of the eighth cervical and the first dorsal segments, oculo-pupillary symptoms occur in a large number of cases. As a rule the paralysis of the sympathetic fibers is unilateral. On the affected side, the pupil is smaller, the palpebral fissure is narrower, and the eyeball is slightly retracted. Ptosis of the eyelid is only apparent and disappears when the patient looks upward. Cocaine causes sluggish or no dilatation of the pupil on the affected side.

Syringobulbia: Cases in which the lesion is restricted to the medulla occur less frequently. The stress falls mainly on the cranial nerves. Diplopia, eye palsy, nystagmus, facial palsy, atrophy of the tongue, laryngeal palsy and dysphagia are the prominent features. Sensory disturbances in the distribution of the trigeminus are frequently found. Two cases of this type will be described in detail in this report.

Pathology: Cavitation of the spinal cord which is the striking pathologic change may arise in diverse ways. In a number of cases, this defect of the cord is of congenital origin, being due to failure of union of the walls of the primative neural groove. In other cases it is believed that the dilatation of the central canal is acquired through some disorder of the flow of the cerebrospinal fluid. Cavities of the cord may also arise by a process of softening and absorption following hemorrhage, infection and thrombosis of the artery supplying a given area of the cord. Not all types of cavity formation may be regarded as true syringomyelia, for the latter is defined as a progressive pathologic process re-

sulting in cavity formation in the substance of the spinal cord, usually occurring about the grey commissure and associated with proliferation of glia tissue. The view which is accepted by most observers is that the gliosis is the primary process and that the cavity formation is the result of degeneration occurring in the glial proliferation which may be blastomatous in character.

In the following case reports, only the positive findings will be detailed. Sensory charts are provided to facilitate the description of the sensory disturbances in each case.

CASE REPORTS

Case 1. History: R. T., a housewife, aged 45, was apparently well until about six years before the onset of the symptoms which brought her to the hospital, except for some "stomach trouble" some six years earlier and an occasional transient attack of hoarseness. The first symptoms of the fatal illness were in the nature of severe burning pains in the precordial region and in the back. The pain was sharp and radiated to the arms and legs; it recurred at irregular intervals and lasted for varying periods of time. There was generalized weakness, most marked in her legs; her knees would give way at times. She suffered from dyspnea on the slightest exertion. Severe headaches were associated with vertigo. She was losing weight and had marked constipation. Increasing weakness and stiffness of her legs made it difficult for her to walk. About five years later she noticed the loss of sensation in her upper extremities. She felt as if her hands were constantly being cooled. She felt numbness in her lower extremities, more marked on the right side.

Examination: The patient was of small stature, and moderately well nourished. Her face was flushed, and her hands and feet were livid. The gait was spastic. The pupils were unequal, the right being larger than the left; both were slightly irregular, but reacted promptly to light, accommodation and convergence. There was ptosis of both eyelids. The muscles of the shoulder girdle, arms, forearms, and the intrinsic muscles of both hands showed marked atrophy, which was more pronounced on the left side. The muscle power was diminished and the grasp was weak on both sides. The deep reflexes were present at the wrist, elbow and shoulder on the left side, but the triceps and the deltoid reflexes were absent on the right side. The abdominal reflexes were not elicited. The knee jerks were exaggerated on both sides. The ankle jerks were present but diminished on both sides. There was no ankle clonus, but well defined Babinski, Oppenheim, Gorden, and Chaddock responses were obtained on both sides. The muscles on both sides were spastic, and paretic. Joint sensibility was disturbed in the right foot. Touch was intact. Sensation to pinprick was diminished over the trunk, upper and lower extremities, and was more profoundly disturbed on the left side. Sensation for heat and cold was disturbed over the same areas. On the back and left arm heat at 100°F. was mistaken for cold (fig. 1, Chart 1). There was marked scoliosis, and tenderness to pressure over the lower cervical and upper dorsal spine. X-ray examination of the spine showed rarefaction of the bodies of the fourth to tenth dorsal vertebrae. The blood Wassermann reaction was negative. The cerebrospinal fluid was clear, under normal pressure, contained no cells, no excess of globulin, and a negative Wassermann reaction.

The patient died of pneumonia two months later. The diagnosis of syringomyelia was confirmed anatomically.

The noteworthy features of this case are the slight symptoms which were present, and the lack of a more profound disturbance of sensation in the presence of so complete an anatomical destruction of the cord.

Case 2. History: F. G., a young woman, aged 20 years, had been well until fifteen months before she came under observation when she noticed spots before her eyes. For five days she saw double. On awakening one morning she noticed that her left hand felt heavy and

only with the greatest difficulty could she move it. At the same time she suffered from severe pain in her back. The pain was sharp and radiated down her left arm and up to the occiput. The weakness in her left hand gradually extended upward until her entire arm was involved; it became so marked that she was unable to lift her arm at all. A few weeks later she noticed that both her legs were numb and that she was losing power in them.

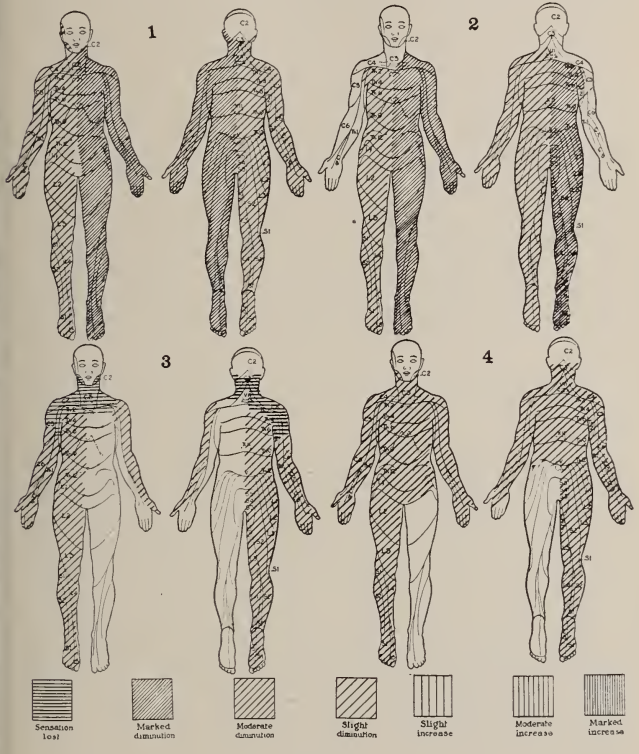

CHART 1

The loss of power was more marked on the left side, and progressively became worse. She also began to suffer from severe drawing pains in all the extremities. She was compelled to drag her left leg and walking became difficult. Somewhat later she received a severe burn on her left shoulder by leaning against a radiator; she felt no pain and did not know she had been burned until the next day when she found her shoulder blistered. She had never before had such an accident. Since the onset of her illness she noticed that the fingers of

her left hand showed a tendency to curl upward. She then experienced numbness and weakness in the right arm. She had suffered from severe constipation since the onset of her illness. During the last two months of the illness she was forced to remain in bed because of weakness of her legs. There had never been any disturbance in bladder control.

Examination: The patient was a poorly nourished, bedridden girl. Her pupils were unequal, the right being larger than the left; they were regular in outline, and reacted promptly to light, accommodation, and convergence. There was ptosis of the right eyelid; enophthalmus of the right eyeball. There was a nystagmoid movement on looking toward the right. There was slight weakness of the right facial muscles. There was a slight prominence over the third and fourth cervical vertebrae, over which tenderness was elicited by percussion. The upper extremities were cold, the hands were livid to the wrists. The muscles were hypotonic. There was marked atrophy of the muscles of the shoulder girdles, arms, forearms, and intrinsic muscles of the hands, more advanced on the left side. The deep reflexes at the shoulder, elbow and wrist could not be elicited. The abdominal reflexes were absent. There was marked hypertonia and weakness in the muscles of the lower extremities. There was generalized wasting of all the muscles of the lower extremities without definite atrophy. The deep reflexes at the knee and ankle were greatly increased on both sides. There was a bilateral ankle clonus and a Babinski sign with all of its modifications. There was a typical sensory disturbance of the dissociative type, extending up to the third cervical segment on the left side, and up to the second dorsal segment on the right side (fig. 2, Chart 1). These disturbances were more marked on the left side and less marked below that level. The blood pressure was 110 systolic and 84 diastolic. The blood Wassermann reaction was negative. The cerebrospinal fluid was under normal pressure; there were no cells, the globulin was slightly increased, and the Wassermann reaction was negative.

An exploratory laminectomy was done and a diffuse intramedullary disease was found. The patient died about one week later. Permission for a complete autopsy was not obtained, but about three inches of the cervical cord were removed. The anatomical diagnosis was syringomyelia.

Case 3. History: B. C., a man, aged 42, had gonorrhea at the age of 18 years. At the age of 24 years he had a throat infection which lasted six months. About six years before coming under observation, he noticed that his voice had become high pitched, and he experienced some weakness in the muscles of the right arm, although it was not enough to interfere with his work. Two years later he began to suffer from numbness and an occasional cramp in the muscles of the right leg. Within another two months he began to experience sharp, shooting pains in the muscles of the right leg. The pain would come on intermittently and was equally severe both day and night. Soon after this he began to have pain in the right groin and in the right shoulder; he also noticed that his tongue was drawn to the left side. Twitching in the muscles of the right leg set in, and the leg became weak. He then commenced to have difficulty in walking. The left leg remained unaffected. He experienced slight difficulty in passing his urine. He also had slight difficulty in swallowing, but never regurgitated fluids through the nose. A girdle sensation around the abdomen appeared. At the beginning of the fifth year of the illness, he began to experience diplopia, associated with occasional attacks of vertigo, and for the last six months tinnitus in the right ear developed; the left leg also became weak and tremulous.

Examination: The patient was well nourished and well developed; he walked with the aid of a cane. The gait was spastic and hemiplegic. The right palpebral fissure was wider than the left. There was slight enophthalmus of the left eyeball. Nystagmus was present in both lateral planes, also on looking upward. It was more marked in the right lateral plane. Corneal hypesthesia was present on the left side. There was weakness of the face on the left side. The tongue deviated to the left; it showed a well marked atrophy and fibrillary twitchings. The pharyngeal reflex was diminished on the left side. There was some atrophy of the left sterno-mastoid muscle. The muscles of the right arm were weak

and hypotonic. Adiadochokinesis was present. The deep reflexes at the wrist, elbow and shoulder were diminished on the right side. The right leg was weak and spastic. Fibrillary twitchings were present in these muscles. The abdominal reflexes were absent. The cremasteric reflex was absent on the right and diminished on the left side. The knee and ankle jerks were increased on both sides. There was bilateral ankle clonus, and a Babinski sign with all its modifications. Sensory examination showed the typical dissociation of syringomyelia. The more intense disturbance being on the right side (fig. 3, Chart 1). The blood and cerebrospinal fluid Wassermann reactions were negative.

The patient died. Autopsy showed the typical syringomyeliac lesion in the cord.

Case 4. History: F. P., a single woman, aged 35, was well until about three years before she came under observation. At that time, she developed sharp drawing pains in her right leg one day after she had jumped from an elevator to the ground, a distance of several feet. The pains were intermittent and would become worse toward the evening. When she arose from a sitting position she would have to rest for several minutes until the pain subsided. Very frequently the leg would swell and then regain its normal contour within three or four days. Shortly thereafter, there developed numbness, coldness and burning sensations in that leg. The burning was particularly severe at night. One year after the onset of the illness she began to have pain and paresthesias in the fingers of the left hand, accompanied by a drawing sensation toward the left shoulder. The left hand and arm gradually became weaker. Three months later the right hand became similarly affected and she had to give up her job as a tailor. The power and ability to do finer coordinated movements had gradually diminished so that she became quite helpless. About this time a hot iron applied to her abdomen in order to relieve abdominal cramps caused a severe, but painless, burn. Her pains and paresthesias were gradually increasing in severity.

Examination: She was a moderately well nourished woman. Marked kyphoscoliosis of the dorsal vertebrae was noted. The right pupil was larger than the left and both responded promptly to light, accommodation and convergence. There was slight ptosis of the left eyelid, and slight enophthalmus of the left eyeball. Sensation of the uvula and soft palate was diminished. There was weakness in both arms and hands, especially on the left side. The muscles of both hands and the left arm showed well defined atrophy. The deep reflexes at the elbow were increased on the right and diminished on the left side. The wrist jerks were absent bilaterally. The abdominal reflexes were not obtained. The knee jerks were exaggerated bilaterally. The ankle jerks were normal. The Babinski sign was positive on the right and questionably present on the left side. The blood pressure was 110 systolic and 84 diastolic. The Wassermann reactions of the blood and cerebrospinal fluid were negative. The typical sensory dissociation of syringomyelia was present (fig. 4, Chart 1).

Case 5. History: A. M., a 34 year old woman, began to suffer from numbness in the left shoulder and weakness of the left hand about four years before coming under observation. Occasionally she experienced a burning pain in the left arm, which lasted for several hours. For a period of two years she had numbness and soreness in the right shoulder, and weakness of the right hand, as well as severe burning and drawing pains in the left hypochrondriac region. This pain was at first intermittent, but later came continuous. She complained of an occasional headache, associated with dizziness. During the last year her vision had become impaired.

Examination: The pupils were unequal, the right being larger than the left; both were slightly irregular, but reacted promptly to light, accommodation and convergence. The jaw jerk was exaggerated. Atrophy and fibrillary twitchings were observed in the muscles of the left shoulder girdle. The deep reflexes at the wrist, elbow, and shoulder were slightly less active on the left than on the right side. The right knee jerk was less active than the left. There was marked tenderness to pressure over the upper cervical vertebrae, with typical sensory dissociation in the areas extending from the fourth and fifth cervical seg-

ments (fig. 5, Chart 2). The blood and cerebrospinal fluid Wassermann reactions were negative. The cerebrospinal fluid was under moderately increased pressure and contained six cells.

This case represents a very early type of cervical involvement.

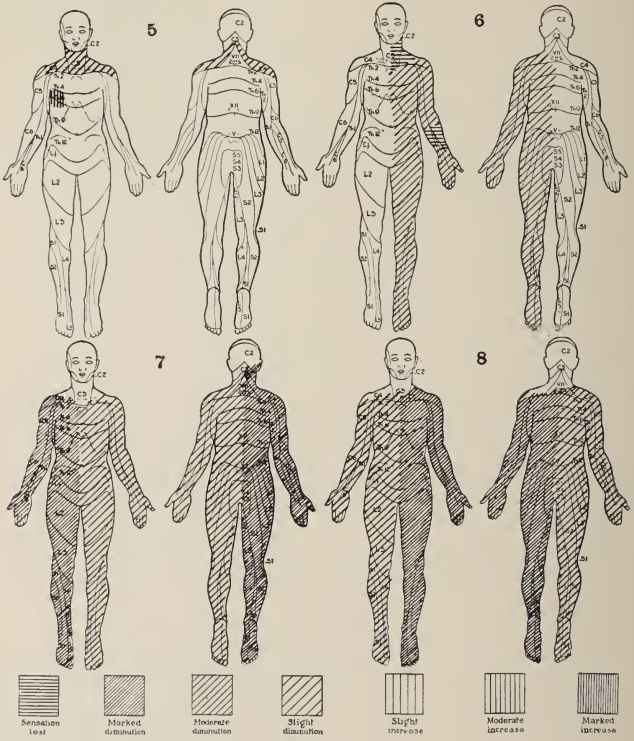

CHART 2

Case 6. History: A. G., a 36 year old woman, noted burning pain in the dorsal region of the spine and drawing pains which extended to the left upper extremity about eighteen months before she came under observation. Paresthesias were present in the left arm. The muscles about the shoulder gradually became weak, and the weakness progressed until the patient was unable to raise her left arm to a right angle.

Examination: The pupils were unequal, the right being larger than the left, but both were regular and reacted promptly to light, accommodation and convergence. Congenital

strabismus was present. Slight hypesthesia of the left cornea was observed. The tongue showed fibrillary tremors. There was weakness of the sterno-mastoid and the trapezius muscles on the left side, as well as of the latissimus dorsi, deltoid, biceps, and triceps muscles. Atrophy of the thenar and hypothenar eminence of the left hand with fibrillary tremors in most of these muscles were present. The left biceps and triceps reflexes were diminished. There was tenderness over the cervical vertebrae. The knee and ankle jerks on the left were more active than on the right side. Sensory dissociation was present over the entire left side (fig. 6, Chart 2). The blood and cerebrospinal fluid Wassermann reactions were negative. The urine showed a trace of albumin.

This case also illustrates early cervical involvement in syringomyelia.

Case 7. History: D. C., aged 40, experienced stiffness and weakness in the muscles of his left leg as well as difficulty in walking for about one year before coming under observation. At that time he developed drawing pains and paresthesias in the left shoulder and arm. Later, weakness of the left arm and hand appeared. The difficulty in gait rapidly increased. He had urinary frequency and constipation.

Examination: The patient was a well nourished man, who walked with a hemiplegic gait. The left arm was held in a typical hemiplegic attitude. Tenderness to pressure over the cervical and upper dorsal vertebrae was noted. There were present marked fibrillary twitchings in the shoulder girdle muscles of both sides accompanied by wasting. The muscles of the left arm were hypertonic. The deep reflexes at the wrist, elbow and shoulder were exaggerated. There was a tremor of the left hand with clonus of the wrist. The abdominal reflexes were diminished on both sides. There was marked weakness of the muscles of the left lower extremity without atrophy. The knee and ankle jerks were more active on the left side. Bilateral ankle clonus and Babinski sign was present. Typical sensory dissociation on both sides below the level of the third cervical segment was discernible (fig. 7, Chart 2). The blood and cerebrospinal fluid Wassermann reactions were negative.

This case represents a very rapidly progressive process beginning in the cervical part of the cord.

Case 8. History: X. F., a 33 year old man, had colitis, followed by anemia during childhood; malaria in early adult life; and three attacks of gonorrhea. At the age of 22 years he began to have difficulty in walking because of weakness of the left leg. This became so marked he could scarcely lift his foot from the ground. At the same time he also began to suffer from obstipation. During the next three years there was progressive stiffness of the left leg. With the loss of his father, which distressed him considerably, he began to suffer from severe generalized headaches. He also noticed that his left arm was becoming weak and stiff with finer movements of the fingers gradually being lost. Sometime later the right leg became involved and the patient had to use a cane to aid him in walking. Six years after the onset of his illness he began to have double vision on lateral gaze. He also began to suffer transitory attacks of vertigo. Occasionally he experienced difficulty in swallowing solids, but did not regurgitate fluids through the nose. After an attack of influenza the symptoms became aggravated.

Examination: The patient was a poorly nourished man. He walked with a spastic paraplegic gait, and favored his left leg. His voice was high pitched and monotonous. The pupils were unequal, the left being larger than the right; both were irregular, but reacted promptly to light, accommodation and convergence. There was marked nystagmus on upward gaze and to either side. Corneal hypesthesia was present bilaterally. Weakness of the facial muscles was noted on both sides, and the tongue deviated to the left, displaying some atrophy and fibrillary tremors on that side. Pain sense was diminished on the soft palate with some areas being completely anesthetic. The muscles of the left shoulder girdle showed marked atrophy. Muscle tone was increased on both sides, the power was poor, the finer movements were awkwardly performed. The deep reflexes at

the wrists, elbows, and shoulders were much increased. The abdominal reflexes could not be elicited. There was marked spasticity, hypertonia and weakness of the muscles of both lower extremities. The knee and ankle jerks were markedly increased. Bilateral ankle clonus was elicited and a Babinski sign was obtained. Sensory dissociation was present on the palate, trunk and all extremities, more pronounced on the left side (fig. 8, Chart 2). Electrical reactions showed diminished responses to Faradism on both sides. The blood and cerebrospinal fluid Wassermann reactions were negative. X-ray examinations showed marked fibrosis of the periarticular tissues of both knees and small joints of both hands. There was pronounced atrophy of the long bones of the lower extremities. There was a moderate curvature of the upper part of the dorsal spine to the right.

Case 9. History: M. U., a young man, aged 22, was apparently well until three years before coming under observation when he experienced the sudden onset of severe pain in

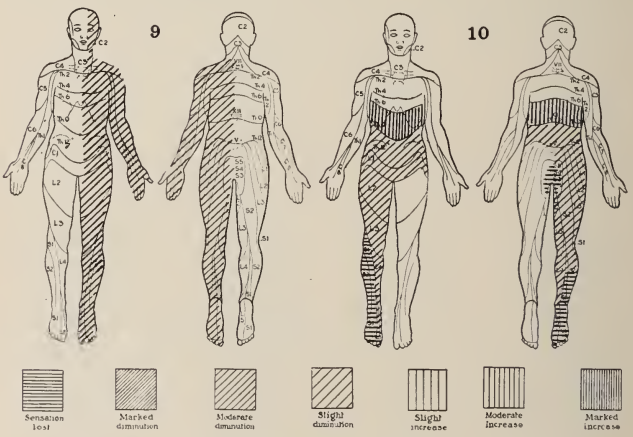

CHART 3

the left ankle and a sensation of pins and needles in the left foot. This sensation gradually spread to involve the left leg and arm. There was a sensation of heaviness and coldness in the two extremities. This lasted for two weeks and then he noted that in attempting to walk he would tend to fall to the right. He had an occasional attack of vertigo. About one year later the left side of his face became paralyzed, and he had an attack of diplopia which lasted two days. His tongue deviated to the left. Swallowing and speaking became difficult, but this improved after six weeks. Shortly thereafter he began to experience excessive sweating on the right side.

Examination: The patient was a well nourished man. His skin was greasy and moist on the right side. His hands were cyanotic and cold. The pupils were unequal, the left being larger than the right; both reacted promptly to light, accommodation and convergence. There was ptosis of the left upper eyelid. There was marked weakness of the left external rectus and the superior oblique muscles. There was a coarse nystagmus present on looking in both lateral planes. There was corneal hypesthesia on the left side. There

was complete paralysis of all three branches of the left facial nerve. The tongue deviated to the left, and it showed marked atrophy and fibrillary tremors on that side. The pharyngeal reflex was diminished. The left half of the soft palate did not elevate as well as the right. Muscle power was slightly diminished in the left upper and both lower extremities. Muscle tone was normal and there was no atrophy or fibrillary twitchings. The deep reflexes were diminished at the wrist and elbow, with the exception of the triceps jerks which were normally active on both sides. The abdominal reflexes were present on the right, but absent on the left side. The cremasteric reflexes were absent. The knee and ankle jerks were slightly more active than normal, but no ankle clonus or Babinski sign was obtained. The patient assumed a wide base when standing and walked with an uncertain gait. There was a slight Romberg sign present. Sensory examination showed diminution of pain sensibility on the left side of the face, while the trunk and extremities showed hypersensitivity to pain. Temperature sensation was diminished over the entire left side of the body (fig. 9, Chart 3). The blood Wassermann reaction was doubtful. X-ray examination showed marked condensation of all the bones, including those of the spinal column.

Case 10. History: C. B., a young woman, aged 27 years, gave a history of retarded physical development. She acquired her first teeth at the age of fourteen months, was able to stand at the age of three months and walked at the age of four years. At that time she passed through an attack of lightning-like pain localized to the small toe of her left foot. A large bleb developed, which broke and formed a penetrating ulcer. The subcutaneous tissues became infected and amputation of the toe had to be performed. This process recurred so many times that nineteen operations had to be performed with the result that she had lost half of the left foot, and two toes of the right foot. At the age of 17 years the patient was burned on her right foot by a hot water bottle and again she suffered from deep penetrating ulcers which were resistant to healing. Until about the age of 26 years she had difficulty in holding her urine and was at times incontinent. She became subject to attacks of pain which would begin in the lumbar region of the back and radiate down the leg until it became localized in the foot. The pain was sharp and stabbing in character. An attack of pain would end in the formation of a bleb in the foot which would break and become infected and involve the deeper tissues. The pain would last from two to three days and then disappear. It was always associated with vomiting.

Examination: The patient was a well nourished woman. She had marked kyphoscoliosis of the spine in the dorso-lumbar region. She walked with a waddling gait. Her pupils were unequal, the right being larger than the left; both were regular and reacted promptly to light, accommodation and convergence. The upper extremities did not show any abnormality in the muscles. The deep reflexes were present and equally active. The upper abdominal reflexes were present but diminished. The lower abdominal reflexes were absent. The muscles of the thighs did not show any atrophy or disturbance in tone. The muscles of the legs showed marked atrophy but no tremors. The knee and ankle jerks were absent. On the right foot, the great toe was partially amputated but on stimulating the sole of the foot the stump would react by dorsi-flexion suggesting a Babinski response. There was a large lipoma in the sacral region of the spine. Sensory examination showed hyperesthesia from the seventh to the tenth dorsal segments. There was hypesthesia below that level, more marked on the right leg and almost complete anesthesia in the fourth and fifth sacral segments with typical dissociation on the right leg in the distribution of fifth lumbar and first sacral segments (fig. 10, Chart 3). X-ray examination of the spine showed a large spina-bifida defect. The blood Wassermann reaction was negative.

This case illustrates one of the congenital types of syringomyelia, but the pupillary involvement, the typical sensory dissociation, the hyperesthesia and the loss of abdominal reflexes warrants the diagnosis of central diffuse gliosis of the spinal cord. Cases 9 and 10 are examples of typical syringobulbia.

HISTOPATHOLOGIC OBSERVATIONS ON THE CHANGES OF THE EYES IN A CASE OF AMAUROTIC FAMILY IDIOCY (INFANTILE TYPE OF TAY-SACHS)[1]

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In contrast to abundant reports on the changes in the central nervous system of patients suffering from amaurotic family idiocy, investigations on the condition of the visual apparatus in this disease are scarce. Wernicke (1) states that only in fifteen cases were the eyes examined. The foregoing pertains especially to the Tay-Sachs or infantile form of amaurotic family idiocy. In cases of the juvenile form, the visual system (the retina, optic nerve and optic tracts) have been studied more frequently. The reason for the scarcity of pathologic reports on the changes in the visual system of amaurotic idiots is that the eyes are seldom removed at necropsy and therefore are not available for histologic observations. For instance, of the five cases of amaurotic family idiocy which I studied, in only one were the eyes removed. This was from a patient of Dr. Roos (2) who reported elsewhere the anatomic and the clinical features of his case.

Immediately after the necropsy, the tissues were placed in a ten per cent solution of formalin; the blocks from various areas were embedded in celloidin, and the sections were stained by various methods—hematoxylin-eosin, Van Gieson, Bielschowsky, Bodian, Alzheimer-Mann and a combined Bielschowsky and Alzheimer-Mann stain.

Unfortunately, the necropsy was performed sixteen hours after death, at which time (and even earlier) some retinal structures usually disintegrate and this renders a proper evaluation of the microscopic changes in them very difficult.

The outer, fibrous tunic consisted of bundles of fibrous tissue with sparse interspaces which were for the most part empty; the middle tunic, the choriodea contained immense amounts of chromatophores mixed with fibroblasts, polyblasts and naked nuclei (oval, round, oblong, kidney-shaped and usually poor in chromatin). Some chromatophores were granular and occasionally resembled grossly ganglion cells. The blood vessels of this layer were, as a rule, dilated and hyperemic, but otherwise exhibited no changes, such as signs of inflammation or new formation of capillaries. Also well preserved was the subjacent pigment layer of the internal tunic, the retina. The cells of this retinal layer were densely packed with brownish pigment and often not only the nuclei but even the cell borders were obscured by the masses of pigment granules.

The next layer, containing the rods and cones, was not available, for, as has been stated, the necropsy was performed sixteen hours after death. Hancock (3), Grinker (4), Haggedoorn (5) found in their cases no changes in them. It should

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be noted that, according to Ramón y Cajal (6), the cones and rods of even normal eyes are subject to early post mortem changes, already several hours after death, while Stargaardt (7) found changes in the cones and rods as early as two hours

FIG. 1. The upper two dense layers of nuclei are the upper and inner granular or nuclear layers of the retina, divided from one another by external plexiform layer containing numbers 3 and 8. These numbers signify nuclei surrounded by some cytoplasm which is particularly abundant at 1, 2, 4, 5, 6, and 7 and is described in the text. Numbers 4, 5, 6 are the ganglion cells of the large ganglion cell layer; these are present also in the inner plexiform layer which appears granular (at 1 and 2) as if packed with the reticular, honeycombed cells (Toluidin blue stain).

after death, when they appear granular and broken up. These formations represent the processes of the neurons, the nuclei of which constitute the external nuclear (granular) layer, called by Cajal the zone of the visual corpuscles. This layer, the upper one in the picture (fig. 1), appeared of normal width; its

cells were arranged in rows and were so thickly packed that no interspaces could be discerned among them. It grossly resembled the inner nuclear (granular) layer which was not so wide and from which it was separated by a light zone, the external plexiform layer. The peripheral endings of its bipolar, horizontal and amacrine cells that make up the inner granular layer are sent to the internal plexiform layer situated beneath the latter. The internal plexiform layer appeared granular in specimens stained with toluidin blue, while the cells of the inner granular layer were morphologically alike, as large dark nuclei. Only at its margins some cells contained an appreciable amount of cytoplasm, while others appeared honeycombed and reticular. They were discerned also in the subjacent inner plexiform layer, but were especially abundant in the large ganglion cell layer. Because of their structure they easily escaped notice,

FIG. 2. Transverse section of the optic nerve. The prolongations from the thickened pia above invade the nerve dividing it into numerous fasciculi densely covered in many places with nuclei. Reproduced under higher magnification in figure 3 (Van Gieson stain).

especially on superficial examination. They appeared bloated and reticular (fig. 1), round or oval and devoid of dendrons, Nissl bodies or any other contents. Their nuclei which were for the most part rich in chromatin were displaced to the periphery. In short, they much resembled the cells seen in cases of amaurotic family idiocy in the brain and spinal cord. Such cells were thus present in those retinal layers that are made up of ganglion cells and their appendages, the inner granular, inner plexiform and the large ganglion cell layers (fig. 1).

Optic nerves and tracts. The optic nerves, in specimens stained by the method of Van Gieson, exhibited distinct fasciculi divided from one another by septa of connective tissue. The septa, prolongations of the pia of the optic nerves, were hyperplastic (fig. 2) and usually contained fibroblasts. The fasciculi into which the nerve was divided consisted of nerve fibers many of which retained

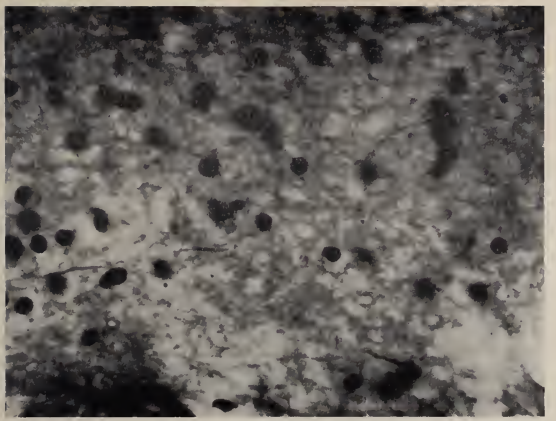

FIG. 3. Optic nerve. A higher magnification of the nuclei (oligodendrocytes and astrocytes) reproduced in figure 2. The field is rarefied exhibiting status spongiosus (Van Gieson stain).

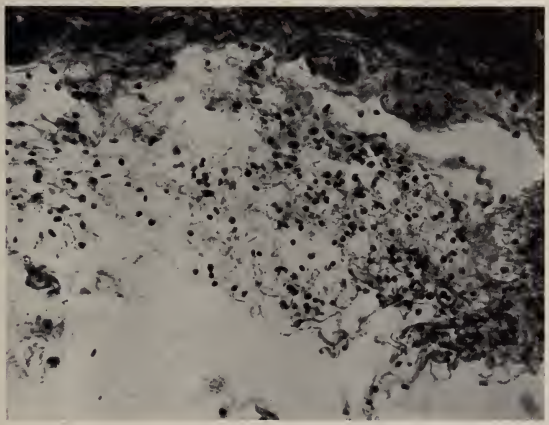

FIG. 4. At the bottom of the picture are longitudinal fibers of the optic nerve. Above the pia-arachnoid enclosing an infiltrated subarachnoid (perioptic) space. Its meshes containing many nuclei are distinct (Van Gieson stain).

their myelin and axons which appeared like balloons or bulbs. Some fasciculi contained rarefied and vacuolated areas. The vacuoles were for the most part empty; occasionally they harbored compound granular corpuscles and gave the visual field the appearance of status spongiosus (fig. 3). The vacuoles were of larger size along the septal prolongations because of shrinkage of the tissues.

Aside from areas of rarefaction, there were in the fasciculi of the optic nerves isolated foci of nuclei (fig. 3). Some nuclei were rich in cytoplasm, and elongated, curved or kidney-shaped, but the majority were devoid of cytoplasm and were poor in chromatin. Some of the nuclei represented oligodendrocytes, others were those of astrocytes (fig. 3) and were abundant in specimens stained by the method of Bodian. The same was true of the optic tract where status spongiosus was marked in the center, while at the periphery many nerve fibers appeared well preserved.

The pial covering of the optic nerve was of unusual interest. In surface sections, paralleling the course of the optic nerve, it was possible to differentiate its perineurial (perioptic) space—between the pia and the arachnoid. The space (fig. 4) contained lymphocytes, fibroblasts, polyblasts and compound granular corpuscles. In some places these elements were numerous, in others, in the thickened septal bands, they were sparse.

COMMENT

The changes of the ganglion cells of the retina were analogous to those seen in cases of amaurotic family idiocy. The cells were entirely devoid of processes and Nissl bodies and in their reticular structure resembled compound granular corpuscles. Regardless of such severe changes in the ganglion cells, many optic nerve fibers did not exhibit massive destruction. Only single nerve fibers were affected, in analogy to what takes place in the brain and spinal cord of cases of amaurotic family idiocy. The status spongiosus of the optic nerves and tracts indicates a severe and rapid nerve degeneration and much resembled a similar condition seen in subacute combined degeneration of the spinal cord. It also resembles a rarefaction of cerebral tissue occurring in edema of the brain.

My specimens did not lend themselves to detailed study of the degenerative states of the ganglion cells and their axons. On the whole, as has been pointed out by the earliest students of this problem (Hirsh (8), Holden (9), Poynton, Parson and Holmes (10) and Sachs (11) himself), the pathologic phenomena in the retina and optic nerve are analogous to those observable in the central nervous system. Sachs at first thought that amaurotic family idiocy is mainly a cortical disease, but further observations convinced him that the ganglion cell changes are universal. A possible exception is the granular layer of the cerebellum which is not changed in amaurotic family idiocy. The same is true of the external granular layer of the retina which seems to be the most resistant.

The nature of the changes, accumulation of prelipoids in the ganglion cells, causing their distention with occasional obliteration of the dendrons and many other features discussed elsewhere would suggest a degenerative process of the ganglion cell. The cells were developed enough to be capable of producing

normal axons, but later because of some metabolic disturbances they break down and ultimately become degenerated. Their further growth becomes arrested and for this reason the term "arrested development" used by Bernard Sachs (11) for this morbid condition, which he afterwards named amaurotic family idiocy, is proper, as shown elsewhere (12). Changed as such ganglion cells are, they are capable of performing their function as evidenced in the patient's ability to breath, swallow and by the normal appearance of the axons ensuing from such cells. Ultimately, some of the ganglion cells perish and the nerve fibers subsequently perish with them—they become degenerated. In this connection Kollar's statement that the macula, i.e., the ganglion cells, are destroyed first and the nerve fibers later is of significance.

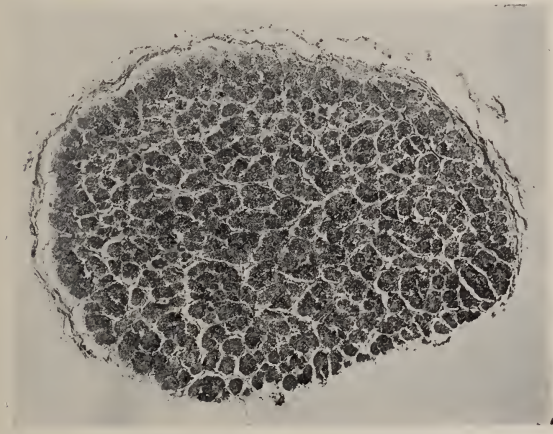

FIG. 5. Optic nerve from a normal child aged 6 months. Should be compared with figure 2. The septa are not as conspicuous as they are in the case of amaurotic family idiocy where they are hyperplastic.

Especially noteworthy are the changes in the septa. These were hyperplastic, in analogy with the hyperplasia of the pia-arachnoid of the membranes of the brain and cerebellum and in marked contrast to normal septa (fig. 5). The thickened septa often showed in their meshes the same cellular elements that were present in the cerebral pia-arachnoid which exhibited hyperplastic thickening in all the five cases of amaurotic family idiocy which I studied. The cerebral membranes contained in their distended meshes lymphocytes, macrophages filled with pigment, compound granular corpuscles packed with lipoids, amyloid bodies, minute granules of free pigment and mesothelial cells. Practically the same elements, including some compound granular corpuscles mentioned also by Haggedoorn (5), were found in the sheaths of the optic nerve

which are pial prolongations. The changes in the cerebral pia-arachnoid have been explained by its reaction to the presence of the aforementioned products in the subarachnoid space to which they are eliminated from the tissues of the brain. That is to say, the pial changes were secondary. In analogy, one may assume that the abnormal products accumulated in the retinal cells are discharged to the optic nerve pia by way of the perineurial or perioptic spaces where they provoke a reaction on the part of the pial septal prolongations. As in the brain, proliferation or hyperplasia of the connective tissue is secondary to the presence of abnormal or chemical discharges, being a reaction to a pathologic condition of the optic nerve. This is not an accidental or a compensatory phenomenon and differs from what is seen in other optic nerve atrophies. In tabetic atrophies, for instance, such a hyperplasia of connective tissue has not been described. According to Stargaardt (7), at the beginning of an optic atrophy in tabes the connective tissue of the septa shows no changes, especially no signs of proliferation. Even in an advanced atrophy, no signs of proliferation were in evidence in his cases and he adds that a significant proliferation of tissue in tabetic atrophy cannot even be considered. On the other hand, in Niemann-Pick disease proliferation of connective tissue though a mild one was found in the optic nerve (Baumann, Klenk and Scheidigger (13)).

SUMMARY

1. The changes in the retina and optic nerves in patients suffering from amaurotic family idiocy are analogous to those in the central nervous system in general.

2. The perioptic spaces exhibit the presence of the same elements seen in the subarachnoid spaces of the brain and spinal cord.

3. The hyperplasia of the pial septa in the optic nerves is analogous to that of the pia-arachnoid, and is a reaction of the latter to the presence in it of abnormal products of activity of the ganglion cells discharged there by way of the perioptic spaces.

4. Status spongiosus, a manifestation of severe nerve destruction, is a striking feature in the optic nerve changes of amaurotic family idiocy.

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SYPHILITIC PAPILLEDEMA WITHOUT INCREASE IN INTRACRANIAL PRESSURE; ITS RELATION TO LESIONS AT THE CHIASM

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In 1937 the condition of syphilitic arachnoiditis of the optic chiasm was described (1). The ophthalmoscopic picture in these cases was of two types: primary optic atrophy, and papilledema.

Most of the cases fell into the first group; similar cases have since been reported (2). These cases, so far as the eyes were concerned, showed: bilateral primary optic atrophy, varying degrees of diminished visual acuity and heteronymous visual field defects. At operation, in each case, adhesions were found around the optic chiasm and nerves.

The present communication deals with the second group, in which the ophthalmoscopic picture is characterized either by papilledema or secondary optic atrophy, and is associated with serological evidence of syphilis and no increase in intracranial pressure. Two cases with this syndrome are herein reported.

CASE REPORTS

Case 1. Acute onset with progressive loss of vision for three years. Frequent episodes of recurring blindness during this period. Bilateral papilledema followed by bilateral secondary optic atrophy. Irregular concentric contraction of visual fields. Visual acuity O.D.: 2/200; visual acuity OS.: 6/200. Wassermann in the blood and cerebrospinal fluid previously 4 plus; colloidal gold 1233321100. Craniotomy. Dilatation of the chiasmal cistern noted and fluid therefrom liberated. Few adhesions around the chiasm. Thickening of the arachnoid. Visual improvement about six and one-half months after operation.

History. L. K., a housewife, aged 37, was admitted to the Neurological Service of Dr. Foster Kennedy at Bellevue Hospital on August 4, 1939. She complained of progressive loss of vision for three years. The onset of this condition was acute. It began three years before when the patient suddenly experienced complete loss of vision in both eyes so that she "could see nothing at all." A few minutes later, her vision returned completely, only to disappear again about four hours later. These episodes of alternating good and bad vision continued for the next three weeks and brought the patient to a hospital on October 7, 1936. On admission to that institution she stated that these bouts of amblyopia had been associated with bifrontal headaches. She gave also the history of a rash developing about two months before the onset of her eye symptoms. The following is a summary of the essential findings noted in the examination at that institution: "The ophthalmological examination revealed bilateral papilledema with an elevation of two diopters on the right and three diopters on the left. Marked secondary changes were seen in the retinae. The right fundus showed engorged veins with lines of exudate converging toward the macula. The left fundus presented a more acute picture marked by flame-shaped and striate hemorrhages; there were also many lines of exudate converging towards the macula. X-ray examination of the skull revealed calcification in the falx cerebri in the posterior parietal region. The blood Wassermann reaction was four plus. The patient refused to submit to a lumbar puncture and was discharged on October 11, 1936. She was put on antiluetic chemotherapy, both intravenous and intramuscular. After a few treatments vision became blurred; the patient stated that it felt as if there was a 'veil' before her eyes."

In March 1937, she was readmitted to the same institution. A lumbar puncture was performed but the cerebrospinal fluid pressure was not noted; the alcoholic antigen was negative, the cholesterin antigen was four plus; the colloidal gold curve was 1233321100. The patient was put on continuous treatment of alternating courses of neoarsphenamine and bismuth. This chemotherapy was interrupted for two months by the delivery of a healthy child. The patient noticed no change in her eyes during or after the pregnancy. She was kept under constant observation in the out-patient department. On July 3, 1939, the blood serology was as follows: alcoholic antigen, negative; cholesterin antigen, four plus; and Kline test, four plus.

Despite the intensive antisyphilitic treatment which the patient had been receiving for eighteen months, her vision had become progressively worse. The patient finally came under the supervision of Dr. Moon-Adams who referred her to us for consideration of chiasmal exploration.

The patient was admitted to Bellevue Hospital on August 4, 1939. Her chief complaint was progressive loss of vision. She stated that the "veil" before her eyes noted above still persisted. She was unable to sew, read or differentiate colors. She gave the added information that the incipient attacks of amblyopia had been associated with headaches, lasting all day and accompanied by nausea, vomiting and the sensation of light-headedness. These headaches disappeared after antileutic chemotherapy. The patient was married twenty years and had four children. She did not know how she had acquired her syphilis. There were no miscarriages or stillbirths. The serologic examinations of her husband and children were all negative.

Examination. Smell function was normal. Visual acuity O.S. 6/200; O.D. 2/200. Color vision was impaired. The patient could not recognize red; only blue could be charted (fig. 3). The visual fields for white showed irregular constriction, partly sector-shaped (fig. 2). Ophthalmoscopic examination revealed bilateral secondary optic atrophy. Both discs were white but the borders were blurred, not sharp. Pigmentation was irregularly distributed around the margin of the discs. The arteries were slightly thinned and accompanied by white stripes. The pupils were of normal size and equal. They both reacted well to light and near objects. The consensual reflex was present in both eyes. The other head functions were normal.

The motility functions in all extremities were normal. The power of all the muscles was good. Point-to-point tests and rapid rhythmic, alternating movements were smoothly and accurately performed. There was no atrophy. The sensory examination for all modalities, including deep pain in the muscles of the calves, was normal. The patient was steady and did not sway when she stood with her feet together and eyes shut. All deep reflexes were active; the right knee jerk being more active than the left. Both ankle jerks were active and equal. The superficial reflexes revealed the following: the abdominal reflexes were present and equal; the left plantar response was flexor; the right was sluggish and occasionally all the toes went into extension.

Laboratory data. Lumbar puncture performed on August 8, 1939, revealed an initial pressure of 105 mm. of water and a final pressure of 80. The cerebrospinal fluid was clear and contained 32 cells, the nature of which was not reported; the Wassermann and Kahn reactions, negative; colloidal gold, 00123322100; protein, 35; Pandy, 0.

On August 29, 1939, an air encephalogram indicated a moderate degree of internal hydrocephalus with dilatation of the chiasmal and interpeduncular cisterns (fig. 1).

X-ray examination of the skull revealed: bones normal in thickness throughout; calcification of the pineal body which was in its normal position; moderate calcification of the falx cerebri; normal sella turcica and normal paranasal accessory sinuses.

Diagnosis. Cerebrospinal syphilis with adhesions at the base of the brain, probably involving the foramina of Luschka and Magendie and possibly implicating the optic chiasm. The diagnosis was also made of a moderate degree of internal hydrocephalus with dilatation of the basal cistern.

Operation. A craniotomy was performed by Dr. Kaplan on September 18, 1939. The

usual transfrontal approach was used to explore the region of the optic chiasm and nerves. The dura was quite adherent to the under surface of the skull. However, on opening the dura, the brain could be easily retracted and a good view was obtained of the optic chiasm. In the surgical procedure the chiasmal cistern was opened and much clear fluid escaped. The optic nerves and chiasm appeared to be somewhat thin. There were but few adhesions, and those that were present seemed to be rather milky in color. A piece of one was taken

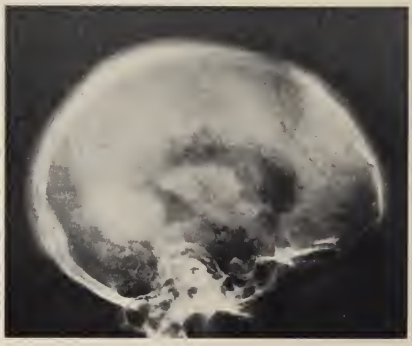

FIG. 1. Case 1. Pneumoencephalogram before operation. Slight internal hydrocephalus with dilatation of the chiasmal cistern.

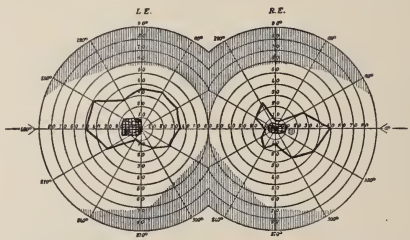

FIG. 2. Case 1. (September 2, 1939). Visual fields before operation. L.E.: Field mapped with a 3-mm. white test object at 250 mm. R.E.: Field mapped with 5-mm. white test object at 250 mm. Visual acuity; L.E., 6/200, recognizes blue but no other color; R.E., 2/200, recognizes blue but no other color. Cross-hatched areas represent absolute scotomata. Visual field could not be charted in the right eye with a 3-mm. white test object.

for biopsy. The specimen was studied by Dr. Lewis Stevenson who found on microscopic examination that the tissue consisted of arachnoid membrane without any evidence of syphilitic arachnoiditis.

Postoperative course. The patient made an uneventful surgical recovery. There was no change in the visual status for some time after operation. However, about six and one-half months later, improvement in visual acuity began to set in.

The progress of visual acuity is charted in Table I. Only in the left eye has there been a definite improvement in visual acuity. In this eye the visual acuity before operation was 6/200; after operation it fluctuated and did not improve until more than six months later when it became 7/200. On October 9, 1940 (more than one year after operation) visual acuity was 9/200; likewise on June 4, 1941 (one year and eight and one-half months after operation) visual acuity was 9/200. In keeping with this progress, the patient stated that she herself had noticed that her vision had improved in various ways: she was able to do her housework again and prepare meals; she was also able to pick things up from the floor without groping, whereas before she had to feel for them.

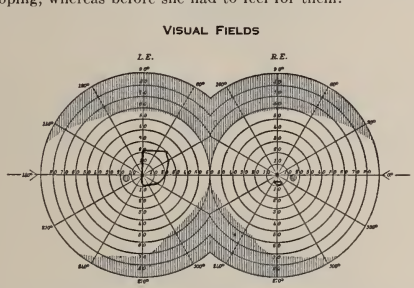

FIG. 3. Case 1. (September 2, 1939). Visual fields for color before operation. Only the field for blue could be charted, for the patient did not recognize other colors. L.E.: Field mapped with a 35-mm. blue test object at 250 mm. R.E.: Field mapped with a 35-mm. blue test object at 250 mm. Field of vision is very small; the test object was recognized in the right eye only in a very small area below the fixation point.

TABLE 1

Progress of visual acuity in case 1

DATE	ACUITY LEFT	ACUITY RIGHT
8- 4-39	6/200	2/200
9- 2-39	6/200 Recognizes only blue	2/200 Recognizes only blue
9-18-39	Operation	
9-29-39	5/200 Recognizes only blue	2/200 Recognizes only blue
10-11-39	6/200 Recognizes only blue	2/200 Recognizes only blue
3-25-40	6/200 Recognizes only blue	3/200 Recognizes only blue
4- 2-40	7/200	2/200
10- 9-40	9/200 Recognizes blue, red, green	3/200 Recognizes blue, red, *not* green
6- 4-41	9+/200 Recognizes blue, red, green	2/200 Recognizes blue, red, *not* green

In the right eye, the visual acuity since operation has neither improved nor receded. This is of interest since the acuity in this eye had been getting rapidly worse up to the time of admission. Before operation the acuity was 2/200; one year eight and one-half months after operation it was still 2/200, although in the interval, on two separate occasions, it had increased to 3/200.

The color perception in both eyes showed no improvement until more than one year after operation, when the patient could recognize blue, red, and green in the left eye, and blue and red in the right eye; whereas, before operation she could recognize only blue in either eye.

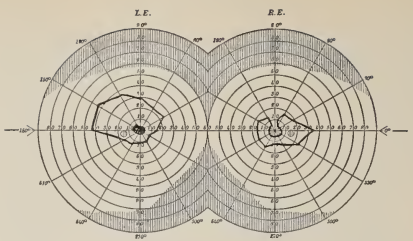

Fig. 4. Case 1. (June 4, 1941). About one year and eight months after operation. L.E.: Field mapped with a 3-mm. white test object at 330 mm. R.E.: Field mapped with a 5-mm. white test object at 330 mm. Visual acuity; L.E., 9/200; R.E., 2/200. In both eyes the patient now recognizes not only blue but also red and green. Cross-hatched area in left eye represents an absolute scotoma, which, compared with that in Fig. 2, is smaller. The scotoma in the right eye is slightly larger.

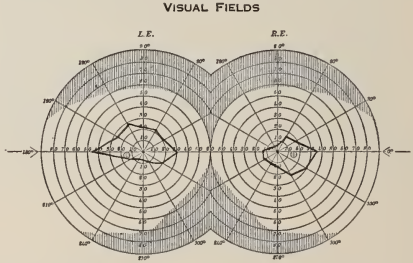

Fig. 5. Case 1. (May 19, 1941). Visual fields one year and eight months after operation. Both eyes charted with a 35-mm. blue test object at 330 mm. Note the marked expansion in the fields as compared with Fig. 2.

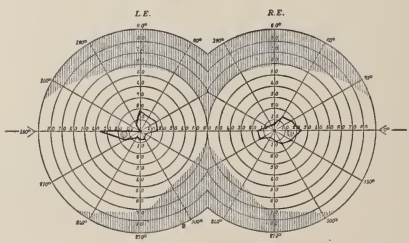

Fig. 6. Case 1. (May 19, 1941). Visual fields one year and eight months after operation. Both eyes charted with a 35-mm. red test object at 330-mm. Before the operation the patient could not recognize red. Was now able to identify also green (35/330) at the fixation point in the left eye, but not in the right eye.

The visual fields are charted in figures 2, 3, 4, 5 and 6. The fields for white, as charted in figure 4 (approximately twenty months after operation), show no improvement; in fact, there has been further contraction and the scotoma in the right eye is slightly larger. The central scotoma, however, in the left eye has improved; it is evident that it is smaller than it was before operation, as charted in figure 2. In contrast to the fields for white, those for blue, as charted in figure 5, show definite expansion one year and eight months after operation. This expansion is very striking in both eyes when compared with figure 3, charted before operation. Furthermore, on October 9, 1940, the patient could recognize, in addition to blue, 17 mm. red and green test objects for the first time with the left eye; and red with the right eye. On May 19, 1941, visual fields for red but not for green could be charted although the patient still recognized a 35 mm. green test object in the left eye at 330 mm. The fields for red are charted in figure 6.

Comment. The history of episodes of sudden blindness, associated with headaches, nausea and vomiting, together with the presence of papilledema, suggested the existence at one time of an internal hydrocephalus probably secondary to a basilar syphilitic meningitis which had partly obliterated the foramina of Luschka and Magendie. Migraine too might account for the headaches. It might also explain the nausea and vomiting in terms of anxiety and tension created by the attacks of amblyopia. The visual disturbance during these episodes might also have been due in part to the migraine. It was felt, therefore, that before treatment could be outlined, two questions had to be answered: 1) was there an internal hydrocephalus; 2) were there adhesions around the optic chiasm. Either or both of these conditions might account for the visual defect. Of the two, the existence of an internal hydrocephalus was considered the more likely. For that reason, the patient was advised that no surgical treatment could be recommended without a pneumo-encephalogram. She refused to submit to this procedure and left the hospital of her own accord. However, she returned several days later and submitted to this test with the results noted above, i.e., slight internal hydrocephalus and dilatation of the chiasmal and interpeduncular cisterns. In view of the pneumo-encephalographic findings and the evidence of a preexisting papilledema, exploration was not advised; the patient was told that the clinical picture which she presented was different from that described in the previous series (1) (characterized by primary optic atrophy and no internal hydrocephalus). It was explained to her that one could not be certain that the surgical procedure, which had been followed in the previous cases, was indicated in her case; that if such a procedure were followed, it would probably not produce sufficient improvement in vision to warrant such intervention. However, the patient, discouraged by the downhill course of her vision and impelled by the fear of blindness, requested to have the operation done. For the first few months following the operation the patient was satisfied that at least the downhill course of her vision had been arrested. However, during this period, we ourselves were not convinced that much had been accomplished by the operation. The conclusion was reached at that time that chiasmal exploration was not indicated in this type of case; a conclusion that has since been revised. The subsequent course of events proved that we had been too pessimistic as to what might be accomplished by surgical intervention in this

case. Now, more than twenty months after operation, the visual acuity in the left eye has improved while that in the right eye has remained stationary. Curiously enough, color perception has improved in both eyes. The visual fields show mixed results. The field for white has not improved but instead shows further contraction; yet, the fields for blue and red show marked improvement. Otherwise, the neurological picture, including the optic discs, has remained unchanged. Whether the visual improvement, thus far observed, would have occurred without the operation is doubtful, for, despite adequate antisyphilitic treatment, vision had been declining steadily over a long period up to the time of operation. In retrospect, the amount of fluid which escaped from the chiasmal cistern, when it was opened at operation, takes on added significance. This will be considered more fully in the discussion later of Heuer's "Chronic Cisternal Arachnoiditis" (4).

The record of this case would not be complete unless it were supplemented by that of another case, previously reported (1). This patient likewise had syphilis and papilledema, but no internal hydrocephalus. Instead, there was a gummatous meningitis at the base, as well as a small gumma of the brain. The record of the case follows.

Case 2. Severe headaches. Positive Wassermann reaction of the blood and the cerebrospinal fluid. Marked papilledema. Concentric contraction of the visual fields. No localizing signs. No increase in intracranial pressure. Antisyphilitic treatment gave no permanent relief. Right subtemporal decompression gave no relief; papilledema remained unchanged. Autopsy disclosed perichiasmal syphilitic meningitis and gumma of the right parietal lobe.

History. J. B., a woman, aged 28, was admitted to Bellevue Hospital on March 14, 1933, complaining of moderately severe headaches on one side for eleven years, which could be relieved by acetylsalicylic acid. Six weeks prior to her admission the headaches became excruciating and paroxysmal and were accompanied by blurring of vision, tinnitus and vomiting. A few weeks before, she had been admitted to another institution for treatment for "meningovascular syphilis," with the following laboratory findings: Wassermann reaction of the blood four plus and of the cerebrospinal fluid two plus; colloidal gold curve 1122321000. Antisyphilitic treatment was administered.

Examination. There were marked bilateral papilledema and concentric contraction of the visual fields, with a tendency to nasal hemianopsia in the right eye. The neurologic examination otherwise was normal. There were no localizing signs or indications of meningeal involvement.

Laboratory data. After antisyphilitic treatment at another institution, serologic reactions were negative, both of the blood and of the cerebrospinal fluid. Lumbar puncture revealed an initial pressure of 280 mm. and a terminal pressure of 140 mm. of water; the cerebrospinal fluid was clear; it contained three lymphocytes per cubic millimeter and gave a one plus reaction to the globulin test.

Diagnosis. It was thought that the condition was due to a basilar syphilitic meningitis with secondary hydrocephalus.

Treatment. Antisyphilitic medication was administered.

Course. The patient returned one year later, with the complaint of progressive loss of vision, especially during the previous two weeks, which was worse in the right eye, and of sudden attacks of "pins and needles" in the left hand, accompanied by dizziness, which lasted from one to three minutes and forced the patient to lie down. In the interval she had received antisyphilitic treatment, which was inadequate. Examination at this time revealed: bilateral papilledema of four diopters; semidilatation and slight irregularity of

the pupils, both of which responded poorly to light but better in accommodation. The visual fields showed greater constriction, with enlargement of the blindspot (fig. 7). Visual acuity in the right eye was 20/60 and in the left eye 20/50. The Wassermann reaction of the blood was negative and of the cerebrospinal fluid plus-minus. Because the treatment had been inadequate, the patient was given antisyphilitic medication, consisting of tryparsamide, bismuth and potassium iodide. The use of tryparsamide was discontinued after three doses, and the bismuth was changed to mercury because of a severe reaction. Repeated lumbar punctures and dehydration were also instituted, but to no avail. A tumor was suspected, and on May 1, 1934, a ventriculogram showed shifting of the ventricular system to the left but no dilatation. On May 7, a subtemporal decompression on the right side failed to relieve the symptoms or to diminish the papilledema.

It was thought at first that the underlying mechanism was a basal syphilitic meningitis which blocked the foramina of Luschka and Magendie, thus producing papilledema with headache. However, the ventriculographic findings indicated no internal hydrocephalus. Furthermore, the cerebrospinal fluid pressure was 160 mm. of water, but seldom, at this time, higher (occasionally 240 mm.). On the basis of these new findings it was postulated that the condition was due to perichiasmal syphilitic meningitis involving the optic nerves.

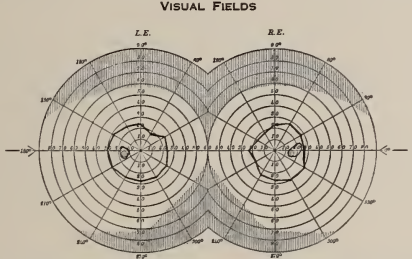

FIG. 7. Case 2. Concentric contraction of the visual fields with enlargement of the blindspots.

While receiving antisyphilitic treatment the patient experienced frequent remissions and exacerbations of headache and vomiting. The papilledema also varied in degree.

The patient was admitted for the third time on September 24, 1934, in a semistuporous state. The long-standing papilledema then showed changes of secondary atrophy. The left pupil was fixed and the right sluggish. There were no definite localizing signs. Paralysis of the abducens nerve was present bilaterally and could be explained by the increase in intracranial pressure. The cerebrospinal fluid pressure was 560 mm. of water; the fluid was slightly xanthochromic and contained 110 cells, 79 per cent of which were lymphocytes. On October 3, a right parietal bone flap was turned down for a possible tumor, which was suggested by the shift of the ventricle to the left. The patient was in a comatose state when taken to the operating room. During the reflection of the flap she went into shock and the surgeon decided not to proceed with the exploration. She died twelve hours later.

Necropsy findings. There was a gumma of the right parietal lobe with perichiasmal syphilitic plastic meningitis. Pathologic examination, by Dr. Lewis Stevenson, was reported as follows: "The cerebrospinal fluid at the base was turbid, and there was a thin layer of fibrin and tenacious muco-purulent exudate overlying the pia arachnoid. This process was most prominent in the interpeduncular space and around the optic nerves." Microscopically, "sections through the optic chiasm stained with hematoxylin and eosin and with Weigert's technique for elastic tissue combined with the Van Gieson method

showed gummatous meningitis in this neighborhood. There was a certain amount of fibrous tissue within the arachnoid, and in a small gumma in the meninges there were a number of large giant cells. Definite endarteritis obliterans was observed in some of the pial arteries, with more or less destruction of the internal elastic membrane in some vessels. There was also periarteritis about many vessels. The exudate consisted of small, round mononuclear cells with scanty cytoplasm, many plasma cells and a large number of phagocytic cells. Within the chiasm itself there was definite syphilitic exudate about many of the vessels, similar in nature to that in the meninges. The microscopic diagnosis was gummatous meningitis of the optic chiasm."

Comment. The papilledema in this case, as in the previous one, was not associated with an increase in intracranial pressure. The latter varied between 160 and 240 mm. of water during the greater part of the illness. The rise of intracranial pressure to 560 mm. of water occurred only towards the end of the disease. That this rise was a terminal event is evidenced by the fact that there was no internal hydrocephalus, despite the fact that the papilledema was of long standing. The loss of consciousness in the late stage of the illness may be attributed to the terminal increase in intracranial pressure.

In the evaluation of the cause of the papilledema in this case, two factors merit special consideration. One is the gumma in the right parietal lobe, the other is the meningitis at the base enveloping the optic chiasm and nerves. Although the gumma may have been a contributing factor in the production of papilledema, it was not the determining one. This deduction is derived from the fact that the subtemporal decompression influenced neither the ophthalmological condition nor the general course of the disease. The mechanism was probably a local one, related to the gummatous meningitis at the base.

DISCUSSION

The clinical picture in these two cases sufficiently resembles that of other conditions to warrant the consideration of the latter for purposes of differentiation. They are 1) syphilitic primary optic atrophy due to chiasmal arachnoiditis; 2) syphilitic hydrocephalus described by Greenfield and Stern; 3) chronic cisternal arachnoiditis described by Heuer; 4) diffuse gummatous meningitis described by Oppenheim; and 5) papilledema without increased intracranial pressure described by Dandy.

The cases of the present series are readily differentiated from those of syphilitic primary optic atrophy due to adhesions around the optic chiasm and nerves (1, 2), by the ophthalmoscopic picture. In the present group the optic discs were definitely choked and when atrophy appeared it was secondary to the papilledema. There was no primary optic atrophy. Pathologically, too, there may be differences. Although, in Case 2, a basilar meningitis enveloped the optic chiasm and nerves and thus resembled the adhesive arachnoiditis of the primary optic atrophy group, no such pathological picture was present in Case 1; instead there was a moderate internal hydrocephalus with dilatation of the chiasmal cistern—a condition which was not found in the cases of syphilitic primary optic atrophy thus far reported.

Differentiation of the present cases from those of syphilitic hydrocephalus provides a more complex problem. In the seven cases reported by Greenfield and Stern (3), the distinguishing features were: syphilis, headache, papilledema and hydrocephalus. Serological evidence of syphilis, either in the blood or cerebrospinal fluid, or both, was present in four of the seven cases. In the remaining cases, the evidence of syphilis was unmistakable at autopsy. Headache was present in all seven cases and was usually the first symptom. It was severe and often accompanied by vomiting and giddiness. Papilledema was present in six of the cases, and in four of them had progressed to optic atrophy. In one case the discs were normal. In two cases blindness set in rapidly, in one of them becoming complete within two weeks after diminution of vision was first noticed. Hydrocephalus was present in all cases. In evaluating the clinical picture, Greenfield and Stern assume that headache was due to an increase in intracranial pressure because of the early presence of papilledema in some of the cases, although no manometric readings of cerebrospinal fluid pressure are recorded. The hydrocephalus apparently was sufficiently marked to warrant the assumption that intracranial pressure was significantly increased. Although these cases of syphilitic hydrocephalus symptomatically resemble those of the present series, there are differences between them, with reference to the degree of intracranial pressure and internal hydrocephalus. In neither Case 1 nor in Case 2 was there a noteworthy increase in intracranial pressure; the rise in pressure noted in Case 2 was a terminal event. Furthermore, there was no internal hydrocephalus in Case 2, while the degree of hydrocephalus present in Case 1 was moderate.

The pathological findings in the Greenfield-Stern group also are pertinent to the discussion. Hydrocephalus together with a basilar gummatous meningitis in the posterior fossa was present in all cases. The investigators were able to make a careful post-mortem examination of the foramina of Luschka and Magendie in four of the cases. They found definite evidence of blockage of the foramina of exit from the fourth ventricle; the cerebellar tonsils were glued down over the medulla and obstructed the foramen of Magendie; the foramina of Luschka were obliterated by meningeal thickening; the fourth ventricle was ballooned out and the cisterna magna was empty. The closure of the foramen of Magendie was probably caused to some extent "by the intense granular ependymitis, which had filled up the calamus scriptorius with newly formed tissue."

Neither one of the cases herein reported resembled those of Greenfield and Stern pathologically. In Case 1 there was no gummatous meningitis and in Case 2 no internal hydrocephalus. In Case 1, in which there was a moderate internal hydrocephalus with dilatation of the chiasmal cistern, no meningitis around the chiasm was disclosed at operation. Of course, there may have been at one time a basilar meningitis in the posterior fossa which partially occluded the foramina of Magendie and Luschka producing an internal hydrocephalus and perhaps an increase in intracranial pressure. However, there was no increase in intracranial pressure while the patient was under our observation.

Pathologically this case more closely resembles the condition described by

Heuer (4) under the title of "Chronic Cisternal Arachnoiditis." In the latter, the walls of the chiasmal cistern are thickened and fluid collects within them under sufficient pressure to cause compression of the chiasm. Heuer reported four such cases; all showed chronic cisternal arachnoiditis with adhesions about the optic nerves; three showed also thickening of the pia-arachnoid with an excess of cerebrospinal fluid over the frontal and temporal lobes. There was primary optic atrophy in three of the cases; only one showed papilledema and this was very slight. It is interesting to note here that visual improvement followed chiasmal exploration of these cases in which the chiasmal cistern was opened.

With reference to Case 2, although it resembles the cases of Greenfield and Stern both clinically and pathologically, it differs from them in that there was no internal hydrocephalus and no increase in intracranial pressure to account for the papilledema. The basilar gummatous meningitis that was present involved especially the optic chiasm and nerves. In this respect it resembles the clinical and pathological picture of diffuse gummatous meningitis described by Oppenheim (5). However, very accurate correlations cannot be made with this group, for, Oppenheim does not refer to the condition of the ventricles or the level of the intracranial pressure in his description of this entity.

Whether the mechanism which produces papilledema in cases of syphilis is general, local, or both, probably depends on the nature of the process in question. Greenfield and Stern state that although headache and papilledema in their cases were probably caused by the internal hydrocephalus, the possibility that the papilledema may have been due to a more local mechanism is to be considered. They comment: "While it is unsafe to suppose that every syphilitic patient who has papilledema is suffering from hydrocephalus, it seems probable that in this series of cases, the papilledema and optic atrophy were due rather to the general increase of intracranial pressure than to meningeal inflammation around the optic nerves."

That a local process might produce papilledema without increase in intracranial pressure is suggested by Case 2 herein reported, in which the gummatous meningitis around the optic chiasm and nerves was most likely the determining factor in the production of papilledema, inasmuch as there was no internal hydrocephalus and no increase in intracranial pressure during the greater part of the illness.

Of special interest is the series of cases of papilledema without increase in intracranial pressure reported by Dandy (6). It comprises forty-four cases. The outstanding symptom in each case was loss of vision—usually a blurring at first. Scotomata, field defects and blindness may develop with great rapidity. The prognosis as to the return of visual function is good. Severe defects of vision and visual acuity, even blindness, may disappear and normal vision return. Blindness remained permanent in only one case. As to the papilledema, it recurred in one case after improving, and that was three years after the initial attack. The underlying etiologic or pathologic factors could not be determined in most of the cases. Two were cases of multiple sclerosis and two of encephalitis; a few appeared to follow a mild nonspecific inflammatory process in the

eye or lids but these cases were definitely in the minority. In only a single case was there a positive Wassermann reaction; it was positive in both the blood and cerebrospinal fluid. This patient gave a history of headache, nausea and soreness of both eyes, duration one month. Vision became blurred two days after the onset of the first symptom and progressed almost to blindness. There was a central scotoma in the left eye. All color vision was lost in both eyes. Visual acuity O.D.: 10/200; O. S.: only light perception. There was a bilateral papilledema with retinal hemorrhages. X-ray examinations of the skull were negative. Ventriculography was normal. Blood pressure was 120 systolic and 80 diastolic. Five months after intensive antisyphilitic treatment, the patient could see as well as ever. Dandy could not be certain that the papilledema in this case was due to syphilis, even though the eye grounds responded rapidly to vigorous antisyphilitic treatment. His reason for doubting this etiologic relationship was based on the fact that the clinical picture in this case so strongly resembled that of the other cases—all without syphilis.

Clinically, the cases herein reported are very similar to those of Dandy's series, especially in the association of papilledema with normal intracranial pressure. Etiologically, they differ from his group with the exception of the one case noted above, in the presence of syphilis, even though the papilledema did not respond to antisyphilitic treatment. Furthermore, Dandy's cases improved spontaneously in the course of a few weeks or months.

Dandy believed that the pathologic process in most of his cases was a local one. It would seem, too, that in the cases of this series the mechanism responsible for the papilledema was a local one. In Case 1, visual improvement set in only after the chiasmal cistern had been opened; it is assumed that there was a local process, as well as internal hydrocephalus, responsible for the papilledema. However, it is fully realized that the evidence for a local mechanism producing papilledema in this case is not incontrovertible. The pathologic evidence in Case 2 is more certain, for the meningitis at the base was thick and gummatous, involving the optic chiasm and nerves. So far as the presence of a gumma in the parietal lobe of this case is concerned, it has already been pointed out that it most likely did not produce the papilledema since there was no internal hydrocephalus, nor any improvement in vision or papilledema following a subtemporal decompression. Why the involvement of the optic chiasm and nerves by adhesions should produce papilledema in this case, and primary optic atrophy in other cases previously reported (1, 2), is difficult to answer. No studies were made of the intraocular tension, or of the diastolic venous and arterial pressures in the retinae of these cases, so that Lauber's (7) hypothesis as to the formation of papilledema, based on these factors, could not be tested.

SUMMARY

Two cases of syphilitic papilledema have been presented: one associated with a moderate degree of internal hydrocephalus, dilatation of the chiasmal cistern and thickening of the arachnoid; the other, with a gummatous meningitis around the optic chiasm and nerves, as well as a gumma of the right parietal lobe. In

neither case was there any significant increase in the pressure of the cerebrospinal fluid.

In the first case, the optic chiasm was exposed and the chiasmal cistern opened. This procedure was followed some months later by improvement in vision. Up to the time of operation, vision had been getting progressively worse over a period of three years, despite adequate antisyphilitic chemotherapy.

In the second case, a subtemporal decompression had no beneficial effect upon the papilledema or visual defect, even in the presence of a gumma in the right parietal lobe. The reason for this failure is attributed to the presence of a thick plastic meningitis around the optic chiasm and nerves, which could have been reached only by the chiasmal route. This surgical approach may be indicated in such cases when conservative measures have failed.

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THE TECHNIQUE OF INSULIN, METRAZOL AND ELECTRIC SHOCK TREATMENT IN PSYCHIATRY

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The employment of "shock" treatment, despite its violent and distasteful nature, is today an accepted mode of therapy for the amelioration of various psychotic and functional disorders. The use of the word "shock" in this connection is unfortunate, and the substitution of the phrase "insulin", "metrazol" or "electric psychiatric treatment" (according to the technique employed), might lessen the aversions of candidates and their families toward these procedures.

At the present time, the usage of these treatments is empirical. Everyone who employs them hopes that their beneficial physiologic alterations may be more fully understood, so that the future may see them induced by less heroic means. Many other relative questions are still in doubt. How much benefit do these measures actually produce? How much of the reported benefit is colored by the operators of a new remedy? What irreversible changes are produced in the brain? Only future research can supply the answers to these and many other allied queries.

INSULIN TREATMENT

The subject to be considered for insulin treatment should have a very careful physical examination, with especial attention paid to the circulatory system. Coronary disease, hypertension, myocarditis and valvular disease are all contraindications. Next in importance are respiratory disorders, with respiratory infections and obstructional conditions constituting the principal bad risks.

The daily administration of vitamin B complex to all patients receiving insulin treatment is highly advisable, due to the important relationships of certain members of the complex (thiamin, riboflavin and nicotinic acid) to carbohydrate metabolism and to the cellular oxidation-reduction reactions.

Careful medical supervision is necessary at all times. During the first hour the physician should be readily accessible, and from the beginning of the second hour until the termination of the treatment he should be in constant attendance.

Unfortunately, standardization of the technique of insulin shock cannot be definitely outlined, and any diagram of procedure can only form a framework within which individual management can be conducted.

Dosage. The variation of insulin dosage is very large and may be from 13 to 600 units. Treatment is initiated by the intramuscular administration of 15 units to the fasting patient. (Large doses of insulin should always be injected deep in the gluteal muscles, as absorption is delayed in the subcutaneous adipose tissue and local necrosis and atrophy may result.)

The course of shock should be conducted and the insulin dosage arranged so

that 1) loss of consciousness should come in the third hour; 2) the Babinski sign should become positive in the fourth hour; 3) tonic, tetanic muscular spasms or central vegetative disorders should appear before the fifth hour. If the dose is too high, these manifestations appear earlier, and if too small they are delayed. Each day the insulin dosage is computed on the basis of the previous day's performance.

Sensitization arises frequently and according to some observers appears in two-thirds of the cases. When sensitization occurs, about one-half of the original dose will produce the desired clinical reaction. Sensitization seems to be influenced by the carbohydrate in the diet, the greater the sensitivity to insulin, and also it is probable that too much fluid may tend to lower the sugar level. Insulin insensitivity is believed to be associated with hyperactivity of the pituitary gland (Flaum). Plattner believes that full remissions are less frequent in the presence of definite sensitization.

In general, doses of more than 200 units are considered inadvisable, and if a larger amount than this is required, methods to reduce resistance should be employed. V. Braunmuhl describes a "zigzag" plan of administration to overcome insensitivity. After insensitivity is determined by a regularized daily increase from the original dosage, he advises giving a maximal dosage of possibly 200 units (which in itself he found unsatisfactory) on one day, and the administration of double the original dose on the succeeding day. This was followed by another 200 unit injection on the third day, then 30 units on the fourth, and so on. This alternation is repeated four or five times. This "zigzag" method frequently leads to the production of coma by much less insulin than was primarily required.

MEDICAMENTS AND DRUGS

The use of the same brand of insulin throughout the treatment is recommended so that reliability of dosage may be expected. Protamin zinc insulin has been investigated as it was considered that it might produce a moderate degree of hypoglycemia of long duration, but in actual tests it has proven unsatisfactory. Administration of insulin intravenously has also been advocated but has proven to have no advantages over the usual method (Jones). McGregor, however, believes that coma is quieter when the insulin is introduced intravenously than when it is given intramuscularly.

Alkalies. Alkaline medication increases the sensitivity to insulin, therefore, alkalies are administered to patients who are resistant. For this purpose one drachm of sodium bicarbonate is given twice daily. Insulin also causes a shift of the hydrogen ion concentration to the alkaline side, and the possibility of alkalosis should be considered when insulin and alkalies are administered concurrently.

Oxygen. In instances where coma is not readily terminated by the use of sugar, oxygen inhalation is employed, the basis of the theory being that brain cells can more readily metabolise carbohydrate in the presence of an excess of oxygen. Inhalation of oxygen is also used in pulmonary edema.

Vitamin B_1. As vitamin B_1 increases the oxygen utilization of the brain cells,

it is indicated when coma is not quickly interrupted. Also in the presence of tachycardia, vomiting and other toxic symptoms 3,000 units (10 mgs.) is given intravenously.

Adrenalin. Adrenalin was formerly advised in continued coma, but has been discarded as it tends to produce motor activity and convulsive attacks, and is therefore considered potentially dangerous.

Calcium. Medication containing calcium has also been advised for use in patients who fail to waken from coma through the usual measures.

Blood transfusion. This has been advised as "life saving" in serious situations.

SYMPTOMATOLOGY

Frostig divides the symptomatology of insulin shock treatment into five groups: 1) Disturbances of consciousness; 2) disturbances of exteroceptive and interoceptive sensitivity; 3) disturbances of motor function; 4) disturbances of the autonomic nervous system; 5) psychotic disturbances.

1. Disturbances of consciousness are divided into sopor and coma. In sopor the speech, thinking and perception are slow, the threshold of psychic reaction is heightened, and there are complaints of dizziness, heat or cold, and altered visual perception. Mental clouding progresses toward coma with slurred, indistinct speech, though strong stimuli may produce temporary clearing and orientation. Loss of consciousness is complete when voluntary motion and speech no longer occur. Coma supervenes when stimuli fail to bring about any reaction.

2. Disturbances of exteroceptive and interoceptive sensitivity follow directly with loss of consciousness and are marked by a lowering of the threshold of response to external and internal stimuli. A bright light or loud noise provokes a quick motor response which later assumes the form of myoclonoid twitchings and athetoid movements. Later when responses to light and noise decrease, movement or stroking of the limbs causes increased muscle tonus or a tonic spasm. When coma supervenes all responses are lost.

3. Muscular hypotonia appears at the end of the first hour and may be accompanied by a fine tremor. Later motor restlessness occurs and consists of purposeless movements of the extremities or primitive movements as sucking, licking the lips, protruding the tongue, scratching, thumb sucking, etc. About the time that consciousness is lost, clonic twitchings appear, occurring first in the muscles of the mouth and chin. Spreading to other facial groups, they soon involve the upper and lower extremities. Tonic extensor spasms are the final form of the motor symptoms, and when they occur the treatment should be terminated or irreversible changes in the nervous system may occur.

Additional complex motor phenomena indicative of disturbances of cerebral functions include: (a) Pyramidal tract disturbances—transient hemiplegia, exaggeration of tendon reflexes, and a positive Babinski; (b) Isolated clonic contraction of the muscles of the face, neck, limbs, hands or fingers; (c) Tonic facial spasms—grimaces, trismus, protrusion of the lips or tongue and spasms of the glottis; (d) Tonic spasms and movements of the extremities and trunk as

pleursthotonous, opisthotonous and emprosthotonous. Movements may occur on one side only, or take pendulum or nutation form.

4. Perspiration, which is viscid early and watery later, is present in 99 per cent of all "shocks" and is one evidence of the autonomic system disturbance. Salivary secretion is almost always increased. Respiration during the first two hours is deep and regular, but with the appearance of the hyperkinetic syndrome becomes irregular and during coma is shallow and slow. The temperature gradually decreases throughout the entire period of shock, except in cases of prolonged coma or other complications, where it may be elevated. High temperatures are of ominous import. There may be profound disturbances of the cardiovascular system. The pulse varies in volume, and the rate in some instances has reached 250 without fatal termination.

Bellet, Freed and Dyer made 59 electrocardiographic studies in patients undergoing insulin shock treatment. In all instances the electrocardiograms were normal before treatment. More or less marked alterations were found in 38 of the 59 studies. These changes include depression of the ST segment, flattening of the T waves, prolongation of the electrical systole (QT interval), P wave changes and slurring of QRS complexes. Auricular extrasystoles, auricular fibrillation, shifting pacemaker and sino-auricular heart block were also evident. The most noted electrocardiographic changes usually coincided with the lowest blood sugar levels, and in most instances returned to normal with the restoration of the blood sugar to normal levels. In some instances two to twenty-four hours were required for the return. The presence of the electrocardiographic changes mentioned are usually considered as evidence of some derangement of the myocardium. The reversible character in these patients suggests that the cause is transient in nature, but shows that the heart bears unusually severe strain during hypoglycemia.

The effects of insulin shock on the eye include horizontal nystagmus in the period before coma, and the loss of tonus of the external eye muscles during the period of deep coma. With each tonic muscular spasm the pupils dilate and lose their reaction to light. When the period of deep coma is reached, the pupils gradually contract, and when they are mere pin-points the reaction to light is lost.

5. Psychotic disturbances are observed in one-fifth of the cases and are usually allied to the patient's own particular disorder. These manifestations occur in the earlier stages and at times in spontaneous wakening. The appearance of these symptoms has been well described by Frostig:

"A survey of symptoms reveals that all signs of insulin effects observed by the bedside are due to changes in the central and autonomic nervous system. No signs of major involvement of other organs are observed. Careful recording showed conclusively that the symptoms develop in a definite sequence. Although many difficulties arise in regard to exact localization, there cannot be any doubt that this order of symptoms is correlated to the phylogenetic structure of the brain. At first those symptoms appear which are to be considered as symptoms of suppression of the cortex. These are followed by signs of release of basal ganglia (hyperkinetic syndrome). Finally the midbrain is suppressed and symptoms due to release of the medulla oblongata (tonic extensor spasms, parasympathetic

syndrome) come to the fore of the clinical picture. In protracted shock suppression of medullary centers is seen."

DIFFICULTIES AND COMPLICATIONS

Nervous system. 1. *Failure to awaken:* The patient should show signs of waking within half an hour after the usual dose of glucose has been administered. Failure to awaken may result from giving the glucose in too concentrated a solution, in which it remains in the stomach and is not absorbed. However, the blood sugar may rise to normal or supernormal levels and the patient may still remain in coma. This condition is believed to result from an inability of the cerebral cells to utilise sugar. The administration of more sugar is useless, and the treatment to be instituted consists of oxygen inhalation, vitamin B_1 and calcium intravenously.

2. *After-shock* may occur when adequate glucose has not been taken. Sweetened fruit juices and other carbohydrates should be given during the afternoon and evening of each day the therapy has been given.

3. *Muscular spasms:* Epileptiform attacks, if they occur early in the course of treatment, indicate overdosage. Convulsions occur in 2.8 per cent of all insulin shocks. The onset is initiated by nystagmus and conjugate deviation of the eyes. No twitchings precede the fit. Tonic spasms then appear and opisthotonous is common. In a few seconds the tonic spasms relax and violent clonic spasms occur. The skin is at first bluish-red, and the blood vessels are distended; with the onset of the clonic phase the color turns to gray. The pupils are dilated and do not react to light. Biting of the tongue is frequent, but involuntary urination is rare. Exteroceptive stimuli do not provoke the fit and have no influence on its intensity.

Respiratory system. 1. *Edema of the lungs* is one of the most frequent complications encountered in insulin shock treatment, and is believed to result from acute insufficiency of the left ventricle, peripheral circulatory failure or obstruction of the air passages, where the heightened negative pressure in the lung is the most significant pathologic factor. The diagnosis of pulmonary edema is made difficult by the restless state of the patient, and the loud râles produced by the accumulation of mucus in the throat precludes accurate auscultatory information relative to the lungs. For the treatment of this condition adrenalin, atropine, coramine, digitalis, caffeine, morphine, dextrose by infusion, phlebotomy and the inhalation of oxygen or oxygen-carbon dioxide mixture are the usual measures recommended. One of the most useful drugs is $\frac{1}{2}$ mg. of strophanthin given intravenously; this drug has been found more suitable than digitalis because of the swiftness of its action. The inhalation of atmospheres rich in oxygen combats the anoxemia and also decreases the negative intrapleural pressure. Adequate but not excessive sedation is useful in removing adverse psychic influences. Codeine is preferable to morphine for this purpose, but should be used with caution in severe pulmonary obstruction. Atropine is of little use. Intravenous injection of 50 per cent dextrose or sucrose solutions is of primary importance. Inhalation of carbon dioxide should be strictly avoided

and a complete removal of it should be accomplished when the patient is in the oxygen tent. Phlebotomy, with the removal of 500 to 800 cc. of blood, is at times dramatic.

2. *Bronchopneumonia* may be caused by aspiration and has been reported as the cause of death in several instances. Robinson and Lamm recommend that the patient in coma should be placed in a flat position with the head turned so as to permit the easy flow of saliva out of the mouth, as it is well known that this position decreases the danger of aspiration. Excess saliva is best removed by suction, and when there is excessive saliva in the trachea aspiration through a bronchoscope may be necessary.

Cardiovascular system. Cardiac irregularities including a pulse rate of either over 140 or under 40 are indications for interruption. As insulin and digitalis have similar effects on the cardiac vessels, digitalis should not be administered to patients taking insulin treatment. If strophanthin is needed in an emergency, it is dangerous to the digitalized heart.

Hemorrhages in the retina and cerebrum have been reported. Acute cerebral edema and hemorrhages with xanthochromic cerebrospinal fluid have been observed. Transient dementia of the Korsakov type has occurred but is very rare.

INTERRUPTION OF SHOCK

The insulin shock treatment is interrupted by the administration of dextrose. The sugar is usually given by nasal gavage unless it is desirable to terminate the insulin effect immediately. When there is vomiting, the glucose is injected into a vein. The usual method of determining the presence of the tube in the stomach is accomplished by the aspiration of a small amount of gastric contents and determining the acidity by litmus paper. Even though the tube is in the stomach, the aspiration of gastric juice is not always possible, and if dextrose has been administered the reaction may not be acid. Attaching a rubber bulb to the free end of the stomach tube, compressing the bulb and listening with a stethoscope for the sound of air escaping into the stomach, is on the whole a more reliable method. When sugar is introduced into the stomach it should not be in too concentrated a solution, as this delays absorption. There is some individual difference in the amount of sugar needed to interrupt coma of moderate severity, but 600 cc. of a 15 per cent solution has usually been found to be satisfactory. Under these circumstances awakening occurs after from ten to thirty minutes. Petrie advises the administration of ten more grams of sugar than the number of units of insulin used. McGregor and Sandison studied the problem of interruption from another angle. Because of the war time rationing of sugar they developed the following method which they believe has definite advantages—the coma is terminated with an intravenous injection of 20 cc. of 33 per cent glucose solution. As soon as the patient regains consciousness, a pint of thin gruel made of mashed potato, milk and water is given. Patients prefer this soup to sugar solution, and the vomiting frequently encountered after the use of sugar is eliminated by the potato soup. Also no cases of late shock are encountered.

INDICATIONS FOR INTERRUPTION

During the period of awakening there is a rapid regression of the symptoms passed through before the induction of coma. On regaining consciousness, the patient is usually euphoric and answers questions readily for a period of ten to thirty minutes, when suddenly or gradually the psychotic symptoms return.

The indications for interruption may be outlined as follows:

1) *Time:* The duration of the entire treatment should not exceed five hours, and deep coma should not continue over one and a half hours or irreversible changes may occur. As a general rule, coma should be interrupted after one-half to three-quarters of an hour.

2) *Neurological indication:* Extensor spasms, convulsive seizure or myoclonic form attack.

3) *Respiratory indication:* Very deep and slow respiration (Kussmaul type), Cheyne-Stokes breathing, or laryngospasm with cyanosis.

4) *Circulatory indication:* Small, rapid pulse, rate over 140 or under 40, definite arrhythmia or signs of circulatory failure.

PATHOLOGY AND PHYSIOLOGY

The pathologic changes observed in experimental animals and in fatal cases of insulin shock are substantially the same. Changes vary somewhat in nature and in distribution. Pathologic differences in the nerve cells are the most constant and present vacuolization in the acute cases, and shrinking and degeneration in the more chronic. In the vessels there is intimal proliferation, with thrombus formation. Hemorrhage, when present, is due to diapedesis, rhexis, leucocytic extravasation and subsequent infarction. Proliferation of the astroglia is always present, but may be either mild and localized or diffuse and extensive. These changes are to a large extent unselective in location, but occur with greatest frequency in the large masses of gray matter of the corpus striatum. These findings are similar to those produced by oxygen deficiency, and it is believed that the alterations described above may well be due to an intracellular anoxia. It is probable that the concentrations of insulin incapacitate the nerve cell to utilize the available oxygen. Himwich gives valid support to this view in his experiments. He administered large doses of insulin to dogs and removed venous blood from the brain and from muscle. Even when the blood sugar fell to very low levels the blood returning from the head was lighter and quite arterialized, indicating that the brain had ceased to maintain normal oxygen consumption during hypoglycemia. Muscle has the ability to oxidize carbohydrate and fat. If the carbohydrate is not available, muscle oxidizes increasing amounts of fat. Brain tissue metabolism is limited to the oxidation of carbohydrate, and when the available carbohydrate declines, the oxygen consumption is reduced, and the energy requirements of the brain are depleted.

The changes in the cerebrospinal fluid are of importance, but are little understood. All observers agree that there is no correlation between the blood sugar level and the clinical symptomatology. The cerebrospinal fluid sugar level is

important, however, as coma does not occur until this level falls (according to Day and Niver) below 35 mg. An instance of prolonged coma has been observed in which the blood sugar was 154 mg., and the cerebrospinal fluid sugar 360 mg. per 100 cc. This discrepancy of ratio of blood sugar to cerebrospinal fluid sugar continued until the patient recovered eight days later.

There also seems to be no constancy in the cerebrospinal fluid pressure, as levels from 10 to over 400 mm. of water are observed. Lumbar puncture seems to have a favorable influence when the pressure is high, but may be dangerous when it is low.

The question of permeability of the cell membrane has received considerable attention, and the general opinion seems to indicate that permeability is increased during hypoglycemia.

THEORIES AS TO THE MECHANISM OF IMPROVEMENT

Theories concerning the mechanism of improvement are not necessarily a subject for discussion in a discourse on technique, but they should be included, as only through an understanding of the *modus operandi* will we be able to improve and supplement our useful measures. A list of the theories include the following: 1) the elimination of diseased cells; 2) changes in the vegetative system; 3) hypoglycemia *per se*; 4) avitaminosis produced by high sugar intake; 5) the production of alkalosis; 6) increase in cell membrane; 7) anoxia, with consequent redistribution of cerebral blood; 8) alteration of tissue respiration; 9) psychologic stimulation; 10) alteration in the secretions of the endocrine glands.

Most of the hypotheses are too vague at present to warrant consideration here. Increase in cell membrane may conceivably lead to improvement in metabolism and function of the brain cells, and this theory has some experimental observations which lead to its support, but it is at present lacking in definite proof.

Anoxia is usually described as of four varieties: 1) the anoxic type, which results from defective oxygenation of the blood; 2) the anemic type, in which there is lowered oxygen capacity of the blood; 3) histotoxic type, in which the tissue cells are altered, so that they are unable to use the oxygen furnished them by the blood; and 4) stagnant anoxia, resulting from slow movement of blood in the capillaries. The work of Himwich referred to previously indicates that in insulin shock there is a diminished cellular metabolism resulting from histotoxic anoxia, while in convulsive therapy the anoxia is of the stagnant type.

However attractive this theory is, there is evidence that anoxia is not the entire cause of the improvements observed in insulin and metrazol treatments. Uncomplicated anoxia has been produced by the inhalation of nitrogen. Reports to date concerning the benefits of this form of treatment are very disappointing.

METRAZOL TREATMENT

"Metrazol treatment" consists in the production of convulsive seizures by the intravenous administration of metrazol (penta-methylene-tetrazol) or cardiozol, as it is termed on the continent.

Pretreatment study should include not only a complete physical examination, but also close attention to the urine, blood chemistry, blood sedimentation rate and electrocardiogram. Previous to the treatment an enema is given and the bladder evacuated. Sedatives such as chloral-hydrate, bromide, paraldehyde or any of the barbiturate group should not be administered during the twenty-four hour period previous to the metrazol therapy, as all of these drugs inhibit convulsions. Delmas-Marsalet, Bergouigan and Lafon report that a rabbit anesthetized with somnifen required forty times the normal dose of metrazol to induce convulsions. Anesthetization with morphine did not raise the convulsive threshold.

On the morning of treatment no breakfast is allowed, dentures are removed and the garments are loosened, particularly about the neck and waist. A pillow is placed over the inferior angles of the scapulae, and a large rubber tube covered with gauze bandage is placed in the mouth. One nurse presses down on one shoulder and checks excessive movement of the adjacent arm. A second nurse performs the same function on the other side. A third nurse exerts pressure on one side of the pelvis and controls the movement of the leg, while the operator carries out the same function on the other side, as soon as the needle is removed from the vein.

The initial dose of metrazol is 0.5 gm. for men, and 0.4 for women. It is injected intravenously in a 10 per cent solution buffered to pH 7.7 with 0.1 per cent disodium hydrogen phosphate to prevent decomposition on sterilization. Injections are usually made every other day, and the dose increased by 0.1 gm. whenever a larger dose is required to produce a convulsion. If the convulsion does not occur within a minute after the first dose, a second may be given greater than the first by 0.1 gm. As long as a dose is effective in producing a convulsion, there is no need for increase in the dose until it fails in therapeutic effect when it is increased by 0.1 gram. The amount of metrazol necessary to produce convulsive seizures has some prognostic significance. Individuals who require over 1.0 gm. seem less likely to show much improvement than those reacting to smaller doses. The fatal dose for man is unknown, but is computed to be 3.0 gms. from animal experimentation data. In the literature there is but one recorded fatality from uncomplicated metrazol poisoning. In this instance 10.0 gm. was taken with suicidal intent.

The convulsive response depends somewhat upon the speed of injection, which should not be less than 1 cc. per second. In order to accomplish this, a rather large bore needle must be used. I have found a number 19 needle, which has an inside diameter of 0.8 mm., to be satisfactory.

The possibility that "speed shock" may play some part in the metrazol shock should receive consideration. "Speed shock" may result from the rapid intravenous injection of almost any substance whether pharmacologically active or inert. The symptoms of "speed shock" include anxiety, flushing of the skin, sweating, tremors, dyspnea, precordial distress, vertigo and vomiting. In serious instances there is severe dyspnea, cyanosis, chills and fever, depression of blood pressure and death. Some observers believe that the bright flushing of the skin which may be the first symptom after metrazol injection, may be due to

this cause, and suggest that when this flushing occurs the subsequent injections should be administered a little more slowly. Pulmonary thrombosis has been observed in animals succumbing to "speed shock" and has also been noticed in fatal instances of metrazol poisoning.

After the convulsions there is a period of confusion which is usually of short duration, but which may continue for several hours. There is total amnesia for the attack, but memory of the injection and subsequent anxiety is acute. Euphoria and eroticism are not infrequent. Vomiting may occur, but is rarely serious.

DIFFICULTIES AND COMPLICATIONS

1. *Fractures and dislocations.* Dislocations of the jaw frequently result from the wide opening of the mouth at the onset of the first tonic phase, but are easily reduced before the patient recovers consciousness. Dislocations of the shoulder also offer very little difficulty. Compression fractures of the thoracic vertebrae have been described, but occur very infrequently if the patient is kept in a position of spinal extension as previously described. Linear fractures of the shaft of the humerus, and intracapsular fractures of the neck of the femur are more serious complications. These two fracture types occur more frequently when the patient is restrained by mechanical means than when some movement is allowed. Restraining sheets, straps, or any form of harness should never be employed. Movement of the extremities should be limited by manual resistance alone. The assistants should be instructed to resist movement, but not to prevent it.

In order to lessen the hazard of fractures, Bennett advises curarization. He prepares an infusion of alchoholic extract from crude curare, and determines the smallest lethal dose per kilo for mice. One-tenth of this dose is used as the initial dose for humans. A sterilized solution of the drug is slowly injected into a vein. Bilateral ptosis, diplopia, strabismus and nystagmus are first noted. Facial masking, weakness of the neck muscles and inability to raise the head follow together with speech disturbance, paresis of the spinal musculature, and later of the arms and legs. The respiratory muscles of the thorax, diaphragm and abdominal muscles are the last to be involved. As soon as paresis is noted in the extremities, the estimated convulsant dose of metrazol is administered. By this method the muscular action is greatly reduced, and fracture complications are almost impossible unless there is pathologic osseous fragility. Gray, Sprading and Fechner report success with this procedure in fifty cases. Some depression of respiration occurred in only three instances, but was satisfactorily controlled by artificial respiration and 1 or 2 cc. of 1:2000 prostigmine methyl sulfate given intravenously.

Burman reports the use of erythroidin as a substitute for curare. This drug is difficult to obtain and to standardize. He found it less effective though less toxic. It was also variable in strength and impossible to obtain in quantities large enough for clinical usage. Rosen, Cameron and Ziegler used beta-erythroidin hydrochloride in doses of 800 to 2400 mg. These workers believed that

this drug may be used with safety, as prostigmine will promptly relieve respiratory embarrassment. The difficulties involved in procuring these drugs and in their standardization necessitates restriction of their use to patients presenting unusual susceptibility to fractures.

2. *Atypical convulsion.* Delayed attacks are usually attributed to delayed absorption caused by some escape of the drug from the vein, or its injection into the subcutaneous tissue. Many instances of delayed and even repeated seizures have occured without evidence of improper injection. Harris and Birnie record an instance of seven convulsions during a period of twenty-four hours subsequent to metrazol injection.

3. *Cardiac disturbances.* Temporary auricular fibrillation capable of continuation for several hours has been reported, but is not serious.

4. *Pulmonary complications.* Pulmonary embolism and abscess are serious complications which may result from thrombophlebitis, produced by the injection. It may be the result of "speed shock", or of aspiration during the attack. Cessation of respiration with severe cyanosis may occur at the end of the tonic phase. Usually respiration will resume normally and spontaneously. If not, artificial respiration, or even pressure on the chest will start normal respiratory movements. Activation of a latent pulmonary tuberculosis has occurred, but should be avoided by proper pretreatment examination, including a blood sedimentation test.

5. *Mental complications.* The most frequent mental complication is a fear and apprehension of subsequent treatment. Many attempts have been made to lessen this apprehension. The usual sedatives—the barbiturates, chloralhydrate and paraldehyde—are unsuitable as they inhibit the convulsive effect of the metrazol. Cook recommends a hypodermic injection of morphine and hyoscine for this purpose. "Summation treatment" consists of an insulin-produced stupor, and a subsequent administration of metrazol. This latter method accomplishes its end.

Many patients develop an amnesia for recent events which may be combined with an apathetic-akinetic type of manifestation. Some instances of Korsakoff syndrome are reported. Fortunately, the amnesia usually disappears within a few weeks after the termination of the treatment. I have not observed, or even seen reported, any permanency of Korsakoff's syndrome, though it has been known to continue for several months.

ELECTRIC CONVULSIVE THERAPY

In order to overcome some of the disadvantages of drug shock therapy, two Italian workers, Cerletti and Bini, introduced the electric method of inducing convulsions. Cerletti had previously conducted experiments on dogs in a study of epilepsy. He produced convulsions in these animals by placing electrodes in the mouth and rectum, and applying shock with an alternating current of 125 volts, applied for a fraction of second.

Shepley and McGregor devised an apparatus which they consider superior to the Italian. These workers use two independent currents: one is a low voltage

direct current for measurement of the resistance of the tissues of the head; the second is an alternating current which passes through a transformer varying the voltage between 50 and 150. Two thousand milliamperes may be delivered, and the time of the shock varied between 0.1 and 0.5 of a second. The electrodes consist of rubber cushion each of which are crossed by four silver plated metal straps. The two electrodes are mounted on an adjustable clamp which allows the electrodes to be applied to the side of the head. The exact point of application to the fronto-temporal region is unimportant, though the anterior portion of the electrodes should not extend beyond the edge of the orbit, and the center of the electrodes should be anterior to the coronal suture. Before application, the electrodes are covered with a thin piece of linen saturated with 20 per cent salt solution. The region of junction of the temporal and parietal bones on each side of the head is well covered with contact paste, and the electrodes are then applied.

When the electrodes are in place, the resistance of the head is measured in ohms on the potentiometer. After the tissue resistance is determined, the alternating current is switched into the circuit and the desired voltage is selected based on the previous resistance record. The time switch is set at the desired time and the shock applied. The exact voltage is largely a matter of experience, as the convulsive threshold does not necessarily parallel the resistance and in practice many workers disregard this measurement.

Many operators commence treatment with a current of 60 to 70 volts and of one-tenth of a second duration. If no attack, or a *petit mal* attack occurs a second attempt may be made, after the expiration of a few minutes, with the same or slightly increased voltage. The usual practice is to increase the voltage by increments of 5 to 10 volts to a voltage of 120 before the time interval is increased. Increasing the time by .05 of a second calls for a reduction of voltage of 10 to 15 volts. One hundred thirty-five volts is usually considered to be the upper limit to be used. In patients who are resistant there are several measures employed to facilitate the production of convulsions. The water content of the body is augmented by excessive intake and by the administration of 1 cc. of pitressin in the morning and in the evening of the day before treatment. Interruption of treatments for ten to fourteen days will usually lower the convulsive threshold.

The physical examination and pretreatment preparation for electric convulsive therapy are the same as those described under metrazol treatment. At the time of treatment, all hair pins should be removed from the hair. As the operator cannot aid in the restraint of the patient one more assistant is necessary. One attendant should control the movements of the head and insure the insertion of the mouth gag. Other assistants resist the forward movement of the shoulders and arms. Two other nurses help to maintain the extension of the spine by maintaining pressure on the pelvis as well as to reduce excessive movement of the legs. Mechanical restraint must be strongly disparaged on account of the fracture hazard. Electroshock therapy is not an office procedure unless a sufficient number of assistants are available.

The convulsion is similar to that induced by metrazol, but as consciousness is lost immediately with the induction of the shock, patients do not experience the distressing preconvulsive apprehension experience with metrazol.

Histologic examinations of animals repeatedly subjected to electric shock treatment fail to reveal any of the pathologic alterations described as resulting from metrazol. No human material has been studied as no fatalities have occurred. Ophthalmologic examination during electric shock discloses a constriction of the arterioles in the fundus of the eye. Constriction of the cerebral vessels may be the cause of the seizure. Reports of experience with electroshock treatment are not as extensive as with metrazol treatment. Workers who have experience with both methods believe that electroshock is as effective as metrazol in producing remission of psychotic symptoms.

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SOLITARY CYST OF THE KIDNEY

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INTRODUCTION

Solitary cysts of the kidney are not rare. In the past six years, twenty-three patients were operated upon for this condition at The Mount Sinai Hospital. Although the pathological lesion was frequently correctly diagnosed, the main indication for exploratory laparotomy was the presence of an abdominal mass. It is important to emphasize that regardless of how sure one might be that a solitary cyst of the kidney exists, it is impossible to exclude malignant renal neoplasm which can resemble it in every clinical and laboratory detail. It is mainly for this reason, in addition to the fact that they do produce clinical symptoms as well as cause destruction of renal tissue, that operation is practically always advisable.

Large single cysts of the kidney were first described by Fahry (1) in 1624. They are a common finding at post-mortem and are estimated by Branch (2) as seen in three to five per cent of all autopsies. This term is distinctly separate from polycystic kidneys or the multiple small retention cysts so commonly found in chronic nephritis. Although most often single and unilateral, from which the name is derived, they can be multiple, bilateral and even multilocular.

GENERAL CHARACTERISTICS

Etiology: There are two theories as to the origin of solitary renal cysts. Kampmeier (3) believed in the congenital theory. In his study of fetal kidneys he found a period in the fetal development which was characterized by the presence of cystic renal tubules. Normally these cystic tubules disappear but their persistence would explain the origin of solitary and polycystic kidney disease. Meland and Braasch (4) believe that the multilocular cyst of the kidney is probably congenital in origin although they state that it can be acquired.

On the other hand, Hepler (5) believes that these cysts are probably of acquired origin. His arguments against the congenital theory are: 1) The unusual onset late in adult life. 2) The frequent sudden onset of symptoms with rapid growth of the cyst. He cites one case where a cyst grew from the size of a baseball to one filling the entire abdomen within nine months and another case where the cyst increased in size from that of a grapefruit to one the size of a full term pregnancy within two months. 3) The rarity in children both clinically and at autopsy. He likewise does not believe that tubular obstruction either at the papilla or due to peritubular sclerosis with contraction with continued secretion into the tubules can cause the large solitary cysts. Hepler's theory of the acquired origin of such cysts is that a lesion which blocks a group of renal tubules and at the same time causes a disturbance of the localized blood supply

TABLE 1

NO.	NAME	HOSPITAL NUMBER	AGE	SEX	SYMPTOMS	PYELOGRAPHIC DEFORMITY	OPERATION	PATHOLOGICAL FINDINGS
1	H. B.	407165	41	M	Epigastric distress	Absent	Complete excision	Solitary cyst size of grapefruit upper pole of left kidney
2	W. H.	436772	44	M	Red cells and pus in urine	Present	Complete excision	Solitary cyst middle right kidney
3	R. E.	438124	46	F	Epigastric pressure, eructations	Absent	Partial excision and carbolization	Cyst lower pole of left kidney
4	B. T.	449236	64	F	Lumbar pain	Present	Partial excision and carbolization	Multilocular cyst lower pole right kidney, double ureter right side
5	R. C.	465500	61	F	Epigastric pain, vomiting	Present	Partial excision and carbolization	Cyst lower pole of left kidney
6	A. H.	468153	46	M	Right lumbar pain	Absent	Partial excision and carbolization	Cyst lower pole of right kidney
7	I. G.		67	M	Prostatic symptoms	Present	Nephrectomy	Large cyst upper and lower poles right kidney, contents 5000 cc., profuse bleeding from kidney after emptying cysts
8	A. F.	438645	60	M	Left lumbar pain	Present	Partial excision and carbolization	Cyst upper pole left kidney
9	A. Z.	404410	67	F	Lower abdominal pain	Absent	Complete excision	Cyst upper pole of right kidney
10	M. L.	402851	59	F	L.U.Q. pain, weakness, loss 10 lbs.	Absent	Complete excision	Cyst lower pole left kidney
11	L. L.	411811	50	F	Pain left flank, loss 23 lbs.	Present	Complete excision	Cyst lower pole left kidney
12	J. A.	416629	68	M	Pain right abdomen	Present	Nephrectomy	Cyst lower pole right kidney intimately attached to pelvis and ureter

TABLE 1—*Continued*

NO.	NAME	HOSPITAL NUMBER	AGE	SEX	SYMPTOMS	PYELOGRAPHIC DEFORMITY	OPERATION	PATHOLOGICAL FINDINGS
13	H. T.	443059	38	F	Epigastric fullness, mass left abdomen	Not done	Complete excision	Cyst lower pole of left kidney
14	C. C.	386419	57	F	Pain left abdomen, loss of weight	Not done	Complete excision	Cyst lower pole of left kidney
15	S. R.	446051	65	M	Prostatic symptoms	Absent	Complete excision	Cyst lower pole of left kidney
16	R. K.	451676	51	F	Gross hematuria	Present	Nephrectomy	Serous cyst lower pole right kidney. Clots in pelvis and ureter due to hemorrhagic pyelitis
17	I. P.	459716	51	M	Epigastric distress	Present	Partial excision and carbolization	Cyst convexity right kidney
18	S. W.	439511	51	F	Mass in each flank	Present both sides	Right side cyst, partial excision and carbolization	Cyst lower pole right kidney. Suspected cyst upper pole left kidney. Not operated
19	A. S.	464542	42	M	Right kidney pain	Present	Partial excision and carbolization	Cyst middle left kidney
20	J. F.	460985	46	F	Pain left flank	Present	Complete excision	Cyst lower pole left kidney. Cyst fluid 1.2 per cent protein
21	R. C.		40	F	Epigastric distress	Present	Partial excision and carbolization	Cyst lower pole right kidney
22	E. E.	423621	40	F	Pain right flank 30 hours, nausea and vomiting	Not done	Nephrectomy	Patient first explored for acute appendicitis or acute cholecystitis and right kidney cyst found. At subsequent operation cyst com-

TABLE 1—*Concluded*

NO.	NAME	HOSPITAL NUMBER	AGE	SEX	SYMPTOMS	PYELOGRAPHIC DEFORMITY	OPERATION	PATHOLOGICAL FINDINGS
								pletely excised. It contained bloody fluid. Frozen section showed neoplasm. Nephrectomy done. Kidney itself no tumor lesion. Myolip-fibro sarcoma
23	I. T.	425642	46	F	Pain R.U.Q. and gastric distress after meals	Absent	Nephrectomy	Hemorrhagic cyst lower pole right kidney. Pathology, papillary adenocarcinoma

to this area is the responsible etiologic factor providing the localized glomerular function continues. He was able to produce experimentally a solitary cyst in a rabbit which did not communicate with the caliceal renal pelvis system.

Structure: The wall of the large solitary cyst is usually grayish-white, from 1 to 5 millimeters in thickness. The inner lining is smooth and the outer wall is independent of the renal capsule although it may be adherent to it. Some describe an epithelial lining to the inner wall while others have found cuboidal epithelium. The wall is composed of fibrous tissue with numerous capillaries. At times remnants of atrophic tubules and glomeruli are present.

Contents: Usually the contents are clear, straw colored and of low specific gravity. Analysis of the cyst fluid shows that it is not urine (Fowler (6)) but closely resembles blood serum or lymph. Occasionally the cyst content is bloody. Although hemorrhagic cysts of the kidney have been separated into a different group, most writers believe that the bloody fluid results from bleeding into the cyst cavity. The presence of hemorrhagic cyst fluid should make one suspicious of the presence of a neoplasm. Thus in thirty-seven cases of hemorrhagic cysts collected by Hepler, ten showed the presence of a tumor within the wall of the cyst. This type of tumor in the wall of the cyst is to be differentiated from a primarily solid neoplasm which has become cystic.

In addition, in a series of two hundred and twelve serous and thirty-seven hemorrhagic cysts, eighty-two cases showed associated lesions in the kidney such as tumor, tuberculosis, anomalies, calculi, hydro- and pyonephrosis, infarct, chronic nephritis and aneurism.

Age and sex: Most cases of solitary cyst occur between the ages of thirty to sixty years. The youngest in Kretschmer's (7) series was sixteen months.

Higgins (8) reported one case in a child three years and two cases in patients between seventy and eighty years. Females are affected twice as often as males.

FIG. 1

FIG. 2

FIG. 1. Case 2. Solitary cyst middle right kidney
FIG. 2. Case 4. Multilocular cyst lower pole right kidney

FIG. 3. Case 7. Double cyst right kidney

FIG. 4. Case 8. Cyst left kidney

Symptoms and findings: Many patients have no symptoms. The finding of an abdominal mass is accidental on the part of the patient or examining physician. Usually the complaints are referable to pressure and displacement of the abdominal organs. There may be vague gastro-intestinal symptoms such as

fullness and distress after meals or constipation. On the right side, biliary tract disease may be simulated. Microscopic and gross hematuria may occur. In one of our cases profuse bleeding occurred from the side of the lesion which filled the renal pelvis and ureter with clots. This was due to an associated hemorrhagic pyelitis (non-bacterial). The mass may be movable and may simulate a mesenteric, pancreatic or even ovarian cyst. Pyelography usually outlines a large kidney shadow with frequently the sharply rounded cyst outline especially if it is located at the lower pole. It may occur at the upper pole or even in the middle and almost split the kidney in half. Deformity of the renal pelvis and calices is commonly present and may be identical with the appearance of the pyelogram due to a malignant renal neoplasm. The function of the affected kidney as determined by the excretion of dyes is usually normal. Quinby and Bright (9) describe three types of cysts.

FIG. 5

FIG. 6

FIG. 5. Case 18. Bilateral cyst of kidneys
FIG. 6. Case 23. Hemorrhagic cyst of right kidney. Papillary adenocarcinoma

1. Simple thin-walled cysts containing serous fluid and do not connect with the renal pelvis or calices.
2. Those which compress and push aside the secretory tissue of the kidney and connect through a small channel with the pelvis or calyx (pyelogenic group)
3. Cysts lying outside the kidney proper and communicate with the pelvis although not really a part of the pelvis.

TREATMENT

We believe that all cases must be explored unless a definite contraindication is present. Frequently when a cyst was suspected, a malignant neoplasm was found and vice versa. We have had two cases of malignant neoplasms within a cyst. These patients frequently have pressure symptoms which can be relieved. One of our cases had 5000 cc. of fluid within the cyst. An additional reason for subjecting these patients to surgery is the prevention of further destruction of renal tissue. The larger these cysts become, the more apt they are to encroach

upon and adhere to the renal pelvis. We believe that aspiration of these cysts through the loin is unsurgical and dangerous.

Although the lumbar approach is preferable, occasionally the mass is approached transperitoneally where it is large or the diagnosis is uncertain. Usually the absence of dilated veins in the perinephric fat is the first clue that a cyst exists rather than a neoplasm. Mobilization of the kidney and a smaller incision can be used if the contents of the cyst are first evacuated by aspiration or by trocar and cannula. The procedures possible are:

1. Excision of the redundant portion of the cyst with carbolization of the part of the cyst wall adherent to the kidney and reconstruction of the kidney with fat underpinned nephrotomy sutures.
2. Excision and enucleation of the cyst which may lead to an accidental opening into the renal pelvis or calyx which should then be separately closed by suture.
3. Nephrectomy is done where there is marked destruction of the kidney, associated lesion necessitating removal of the kidney or profuse bleeding after evacuation of the cyst. This last complication occurred in our patient where 5000 cc. of fluid was removed. The release of pressure caused profuse bleeding both from the kidney and surrounding retroperitoneal tissues.

Convalescence is usually uneventful and there was no mortality in our series of twenty-three cases.

SUMMARY

1. A review of the etiology and clinical features of solitary cyst of the kidney was presented.

2. Abstracts of twenty-three cases operated upon within the last six years at The Mount Sinai Hospital were tabulated. These included cases showing one multilocular, one double, one bilateral and two hemorrhagic cysts.

3. Both cases of hemorrhagic cyst of the kidney were due to neoplasm.

4. One patient with solitary cyst of the kidney had an accompanying gross hematuria due to a hemorrhagic pyelitis.

5. It is impossible to differentiate pyelographically between neoplasm and large solitary cyst of the kidney.

6. Exploratory operation is indicated in all cases of suspected large renal cyst.

7. There was no operative mortality in this series.

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LITTLE SIGNS OF PARATHYROID DISTURBANCE

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In 1912, stimulated by a study by Levy and Rothschild, I published a short paper on the Little Signs of Hemiplegia (Post Graduate M. J., 27: 876, 1912). Whereas the symptoms of a massive hemiplegia are unequivocal and quickly judged those of minimal involvement are not so readily assessed or even at times recognized at all as to their real significance.

I take it that a similar situation may be present as to slight disturbances of the nervous system in parathyroid disorder, although Werner's monograph (Deutsche Ztschr. klin. Med., 1939) does not mention them.

As is well known tetany is a striking symptom of hypocalcemia of parathyroid causation. It is not so widely appreciated that hypercalcemia has a fairly specific syndrome, such as loss of weight, lassitude, weakness and "neurasthenia."

Subtetanic symptoms, however, are much more frequent than is generally recognized, although the increasing study of blood metabolites is bringing them more into the limelight.

As Clifford Albutt once indicated a prevailing custom among medical writers is that of paraphrasic sidestepping of actual autobiography. This small communication will not resort to this subterfuge but will deal with that most interesting of all medical topics "oneself," and more specifically with the writer's parathyroid annoyances.

One of the slighter of such cropped up years ago when I sought to buy a hat. It soon developed that there were none that fitted me to be purchased in the more widely utilized haberdasheries. While I knew, metaphorically, I had a big head and had often been twitted about it at home and abroad, in less metaphoric a sense, to find the proper sized hat was a real, though minor, annoyance. Finally a Stetson $8\frac{1}{2}$ covered the offending dome and this aspect of my quandary was relegated to the background and would not be paraded here were it not for other circumstances.

Happening to visit a roentgenologist for other purposes, he remarked I had a "magnificent Paget skull." While this discovery might have validated this adjective there were drawbacks for this Paget skull had been impinging more and more on my acoustic and vestibular apparatus and deafness and "uncertainty in stance" were among the penalties paid for this "big head," which parenthetically might be said, pertained more to "bone" than "brain."

Searching further for the cause or causes of my "Paget" skull I learned something about certain faulty habits of breathing, in speech, and faulty urge or drive in action. These observations too were recorded and put in print (Tr. Am. Neurol. A., 12: 419, 1923), and affiliations of post-encephalitic respiratory disorders (J. Nerv. & Ment. Dis., 63: 357 et. seq. 1926) discussed (Arch. Neurol. & Psychiat., 16: 627, 1927). Later the factor of "compulsion" in general, and psychoanalytically, received attention. (My "Big Head" was related in some way with "Big Talk."). Inasmuch as my father, among other things, was an elo-

cutionist of no mean quality this respiratory situation seems more than merely accidental. Through imitation, conscious as well as unconscious, I became something more than a stumbling speaker either with prepared addresses and/or with discussions of medical topics (neuropsychiatric) from the floor. Having been gifted or penalized by this capacity, after an early introverted humility that kept me in my seat, I later decided to take every opportunity to have "my say," the which, often accompanied by an aptitude for the humorous, became well known and many opportunities for discussion were embraced to the edification and amusement of my audiences. My medical confreres were insistent upon my being put on the program and I acquiesced and flatter myself that on such occasions there was usually a large audience. Whether such sought for edification or for amusement I would not attempt to differentiate. Probably it was both and since I had allied myself early with the Freudian conceptions, I believe my discussions contained features of interest, both because of the material itself that came up for discussion and for the better oratorical as well as pedagogic methods of my delivery. I had a good voice, could be heard all over the audience chamber.

Thus, from the ages of fifty to seventy, after which time I rarely attended medical meetings, save those of smaller local interests, psychiatry, psychoanalysis and the like. These aptitudes also led to a certain prominence in medico-legal activities where speaking before a jury, I avoided the use of medical technical jargon and spoke in the simpler language of a non-medical audience and became a thorn in the flesh to the counsel of the opposite side of the question.

So much for this feature of exhibitionism which as mentioned, and which with the advancing deafness, partly alleviated by hearing aids, sank into the background of my activities.

But to return to my "muttons," namely the smaller signs of my parathyroid disturbance. There had never been any tetany, nor even tetanoid spasms, but as noted in the previous paper a certain "jumpiness" was evident to myself, if not to my audiences. What was plain to me was an increasing alertness, fairly well controlled, which would tend to make me more than just apt in discussion but the wish to offer a McDuff—"Come one, Come all"-ness. Within myself every statement made by a speaker was met with this critical, if not hyper-critical response, but was repressed and/or suppressed in large part. It was fairly evident to myself at all events there was an urge to get up and at them, with the concomitant striving to wait until I could see the "whites of their eyes"—to fall back upon the old Bunker Hill admonition.

So far as was evident there was no parathyroid adenomas, but there was evident dysfunction. It has not been detectable in the blood chemistry as yet and there are no kidney calculi, though there is a marked increase in the urge to urinate. Roentgen study is again desirable.

Also the intestinal alertness at times made me recall the old "Pluto" joke about "getting younger" but which tapered off "into doing a very childish thing." Once my laundry bore evidence of this quandary and the dosage of cathartics had to be very carefully cut down to a minimum. A Lady Webster, once so efficient and gratifying, had to be halved, or quartered. In fact, no

cathartics were ever necessary. They never had been save for a general formula of a monthly cleansing at the most.

There has been one symptom which I have not seen prominent in any discussion. That has been a peculiar type of skin erethism. At times it would seem as if a single cutaneous fiber would start an electric discharge in a short, sharp, pinch as it were, without any edema or other somatic sign. As if bitten by a flea was as near as I can come to it.

Once I had been to New Orleans and previously I had visited Naples, where these insects held high revel and did not pass by so juicy a morsel as myself. But a flea bite had aftermaths in skin structures, but my flea bites or mosquito-bite-like experiences, never had any visible somatic accompaniments. They were rare phenomena but acute enough for a split second. My nares and cheeks seemed to be sites of special predilection. A flash in the pan and it was finished, sometimes daily, again not for weeks, and probably had environmental psychical concomitants, not analyzed then or since.

From my analytic study of unconscious processes it would not be deemed fantastic if I conceived of these "arrows of outrageous fortune" as petty pin pricks rather than as arrows, but the hyperdermesthesia was there none the less and here conceived of a parathyroid hyperesthesia involving skin structures, somewhat analogous to the other hypercathected organs, the bladder and intestines. Why the special sites of election would need some unconscious material to orient. Thus far all such clues have been lacking or unrecognized. Save a few of the intestinal ones affiliated in some manner with hostile impulses—hurry, hurry, hurry. So much to deliver and so little time left. No wonder so many people wish a hereafter to finish what they hope to do in the now and here. After an adolescent religious conversion, closely related to finding my love object, and a few years of Sunday school activities, the realities of home building, providing for five children and other relations gradually brought such to a minimum and my psychiatric work became more and more engrossing, especially since finding the psychoanalytic procedure drove me nearer and nearer to the realities of the unconscious. Psychiatry now ceased to be Kraepelian and more patterned after Bleuler's Freudian conceptions. These I came to through much intimate contact with Drs. W. A. White and A. A. Brill to both of whom I owe a debt of no mean magnitude.

Dr. White in earlier years, usually spent a month for many summers at my country home, and Dr. Brill labored with me at the Neurological Institute where we were both on Dr. Pearce Bailey's service. Thus, when Dr. Brill brought me a translation of Jung's Psychology of Dementia Praecox for the Monograph Series which Dr. White and I had started, there was now no turning back and we published it. In the years following 66 volumes along related lines were sponsored by the Monograph Series.

In 1897 the purchase of the Journal of Nervous and Mental Disease offered gratification for my acquisitive desires for psychiatric literature and as it was the official organ of the American Neurological Association, though never financially supported by this Association, added materially to the hurry, hurry, impulses already driving me. Then when the Solons of this Association began to

show annoyance at the inclusion of psychoanalytic material Dr. White and I made a clean break and in 1913 inaugurated the Psychoanalytic Review. I am happy to say that although Dr. Sachs never quite came along, he was sympathetically critical only. That the time was ripe is evidenced by the fact that now in its twenty-ninth volume it has always supported itself.

Even though it brought more burden to my productive capacities, already overburdened, its continued success and prestige have in part alleviated these by helping to pay for a secretary, without whose handiwork, devotion and loyalty I could not have handled all that I attempted to accomplish.

Meanwhile the parathyroid demands had something to do with other annoyances chief of which in 1924 was the beginning of an auricular fibrillation. A stop, look, and listen procedure that soon cut out some, then all, muscular activities. Even walking, which had once included mountain climbing, proved burdensome, and thus, more and more scribbling.

What part the parathyroid dysfunction plays in this cardiac disturbance I have thus far been unable to formulate, but hope to be able to make a contribution to it.

Unfortunately, I had not the slightest gift for writing, in the literary sense. My insight into unconscious processes so well utilized by Thomas Mann and others in literary production, lacked the constructive form of the novelist. While I had read widely and deeply, I was unable to put my thoughts into the popular form of even the poorest novelist. Book reviewing was as high as I could ascend along such lines. Inasmuch as both Journal and Review received many books for review there was plenty to do at the lower level.

I had retired from office practice and came to live at my lake home at Hulett's Landing in the lower Adirondacks. A wise annuity scheme suggested by this same helpful secretary put me if not on, next door to "Easy Street". Here I could carry on my work with the Journal and Review at my leisure as for the most part I had adequate housing and help and plenty of books to read or to review. Sometimes this latter task was a chore, but on the whole I enjoyed it. As foreign books began to come in smaller and smaller numbers there was less drive to keep abreast of the self imposed task hence less call upon my phosphorus metabolism in this particular respect. Being practically shut off from laboratory workers I could not check up on my blood chemistry nor get good x-ray pictures. Absence of pain as noted was some evidence that parathyroid osteolytic processes were not very active. Furthermore, the trip of 500 miles to New York and return was not relished. I had done it often in younger days but at 75 it was an awful bore. So I stick to my scribbling watching the female contingent wrestling with their knitting needles. A 40 mile trip to a cinema is indulged in as much as possible and for the sake of the "help" as much as for my own amusement.

The hypercathected bowel and bladder are under control with a barbiturate if demanded, so I carry on but always with the sense of hurry, hurry, hurry, especially at this turn of the year period when holiday festivities seem to interfere with more sober pursuits.

Thus my little squib comes to an end with the conviction of its inadequacy.

THE MAMMALIAN HOMOLOGUES OF SOME DORSAL THALAMIC NUCLEI OF REPTILES

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(*Respectfully dedicated to Dr. Bernard Sachs*)

In comparative anatomy it is customary to divide the diencephalon into three parts: epithalamus (or ganglia habenulae), thalamus proper and hypothalamus. In embryos, the thalamus proper is separated from the epithalamus by sulcus diencephalicus dorsalis, from the hypothalamus by sulcus diencephalicus ventralis. It may be subdivided by Herrick's sulcus medius thalami into a dorsal and a ventral thalamus. In adult mammals this groove usually disappears but the limits between these two parts are fairly well indicated by the lamina medullaris externa thalami.

The ventral thalamus is frequently called subthalamus (not to be confused with the hypothalamus), one of its chief nuclei being corpus subthalamicum of Luys. Other important centers in it are the frontal poles of substantia nigra and nucleus ruber. As is well known these subthalamic centers are concerned with extrapyramidal motility. They are connected with fibers arising from the corpus striatum, especially from its oldest part: the paleostriatum or globus pallidus of mammalian anatomy. Although ascending systems are not lacking in it, the ventral thalamus or subthalamus is intercalated chiefly in descending systems.

On the contrary the dorsal thalamus is largely (but not only) intercalated in ascending systems. The thalamic ascending systems first appear in Amphibia (Rubaschkin, Herrick) where, however, they are still poorly developed. Their increase in reptiles, birds and mammals is the most characteristic feature of cerebral evolution.

The ascending systems of the dorsal thalamus may be divided into neocortical projection centers and striatal projection centers. The former are most evident in mammals, where the ever increasing neocortex prevails more and more over the more stable striatal structures. As a consequence, in higher mammals the striatal projection centers of the dorsal thalamus are hidden under an overwhelming mass of neocortical centers. In reptiles, however, where the neocortex is practically absent, the striatal projection centers of the dorsal thalamus are very distinct. They are connected with a part of the striatum which, in contradistinction to the older predominant efferent part (the paleostriatum), we called *neostriatum*. This neostriatum, not yet present in Amphibia, is well developed in lizards, serpents and especially crocodiles.

Since the neocortical projection systems are practically absent in these animals the neo-striatal projection systems may be far more easily studied in reptiles than in mammals. Once knowing their relations in reptiles it might be easier to trace them in mammals. This was one of the problems which fascinated me when working on the evolution of the corpus striatum in 1907–8

in Edinger's laboratory at Frankfurt am Main. It has ever since kept my interest, and this interest has increased since the thalamic nuclei themselves have recently been investigated in America by Dr. Crosby and her collaborators, in England by Le Gros Clark, e.s., in Belgium by d'Hollander e.s., and in Holland by Winkler and J. Droogleever Fortuyn.

In the reptilian dorsal thalamus, Edinger and de Lange distinguished several centers. The most important of these centers, apart from the lateral geniculate nucleus, were indicated by these authors as the *anterior* and *round nuclei* and *nucleus reuniens*.

The two former nuclei occur in all reptiles; *nucleus reuniens* is especially evident in crocodiles (fig. 1; see also Huber and Crosby). It is present in lizards but its constituent parts either are entirely separate or hardly join in the midline so that it is not a real midline nucleus but is represented *bilaterally*, the nuclei of the two sides bulging slightly into the ventricle and touching each other occasionally (fig. 2). In turtles there may be a union in the midline, though not so conspicuously as in the crocodile. Frederikse working on the lizard called this ununited nucleus the ventral nucleus, a mere topographical indication. As it lies medially under the nucleus *rotundus*, it might also be called *subrotundus* or *paramedialis*.

The names chosen by this observer for this and the other nuclei (apart from the lateral geniculate) did not involve any homology with homonymous nuclei in other animals. They were merely chosen to indicate their form or position in the reptilian dorsal thalamus. Huber and Crosby, in their work on the alligator, made a further distinction in the so-called anterior nucleus, which they rightly divided into a medial small-celled group (*nucleus dorso-medialis anterior*) and a lateral large-celled group (*nucleus dorso-lateralis anterior*). They furthermore distinguished a cell group, lying more laterally and ventrally, in front of the lateral geniculate as *nucleus ovalis*. This last group was recognized by Addens as being the homologue of *Bellonci's nucleus* of the amphibian brain.

In the following discussion we shall omit the lateral geniculate nucleus, which receives some optic fibers and collaterals (and in our opinion corresponds to the mammalian ventral part of the lateral geniculate), and Bellonci's nucleus, which lies between the olfacto-habenular and optic systems. The homologue of this latter nucleus has recently been described by Miss Gilbert in the human embryo and by Addens in the rabbit. The questions we shall deal with in this paper are the mammalian homologues of the dorso-medial and dorso-lateral anterior nuclei of Huber and Crosby, of the nucleus rotundus, and of the nucleus subrotundus or paramedialis and its confluent component, nucleus reuniens.

As far as concerns the small-celled dorso-medial anterior and large-celled dorso-lateral anterior nuclei of Huber and Crosby, comparative studies of the reptilian and lower mammalian thalamus have convinced me that the small-celled dorso-medial anterior nucleus is the homologue of the *nucleus parvocellularis anterior** of mammals described by Gurdjian and Rioch in rodents and

* It is probable that the author has reference here to the nuclear gray usually termed nucleus paraventricularis anterior.—Ed.

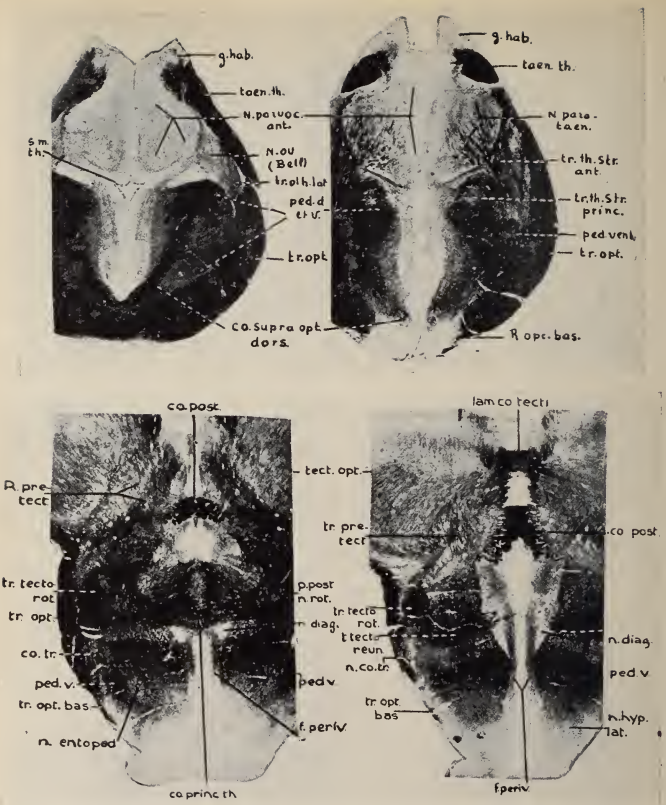

FIG. 1. Series of transverse sections of the thalamus of Crocodilus porosus. C.g.l. = corpus geniculatum laterale; Co.post. = comm. posterior of the midbrain; Co.princ.th. = comm. principalis thalami; Co.supraopt.dors. = comm. supraoptica dorsalis (Meynert); C.tr. =comm. transversa or supraoptica ventralis (v. Gudden); ep.sec. = secretory ependyma; f.periv. = fibrae periventriculares; f.retr. = fasc. retroflexus; lam.co.tecti = lamina commissuralis tecti; n.co.tr. = nucl. commissurae transversae; n.diag. = nucl. diagonalis of Huber and Crosby (= nucl. magnocellularis tegmenti of Frederickse); n.entoped. = nucl. entopeduncularis; n.hyp.lat. = nucl. hypothalami lateralis; n.ov.Bell = nucl. ovalis (= nucl. Bellonci); n.ovoid. = nucl. ovoidalis; n. parataen. = nucl. parataenialis (= dorso-lateralis anterior Huber and Crosby); n.parvoc.ant. = *nucleus parvocellularis anterior (= dorso-medialis anterior Huber and Crosby); p.post.n.rot. = pars posterior nuclei rotundi; ped.d. = pedunculus dorsalis; ped.v. = pedunculus ventralis; R.pretect. = regio pretectalis; S.m.th. = sulcus medius thalami; st.n.co.tr. = stilus nuclei comm. transversae; t.ep. = stilus epiphyseos; taenia th. = taenia thalami; tr.opt. = tractus opticus; tr.op.bas. = tractus opticus basalis; tr.pretect. = tractus pretectalis; tr.tecto-rot. = tractus tecto-rotundus (et-parataenialis); tr.th.str.ant. = tractus thalamo-striatalis anterior (from the nucl. parataenialis); tr.th.str.princ. = tractus thalamo-striatalis principalis (from the nucl. rotundus). The two latter tracts form the dorsal peduncle.

carnivores respectively and by Suzuki in Xantharpyia. Both the dorso-medial anterior nucleus of reptiles and the parvocellular anterior nucleus of mammals (Xantharpyia specially) have a more or less semicircular shape, their flat side

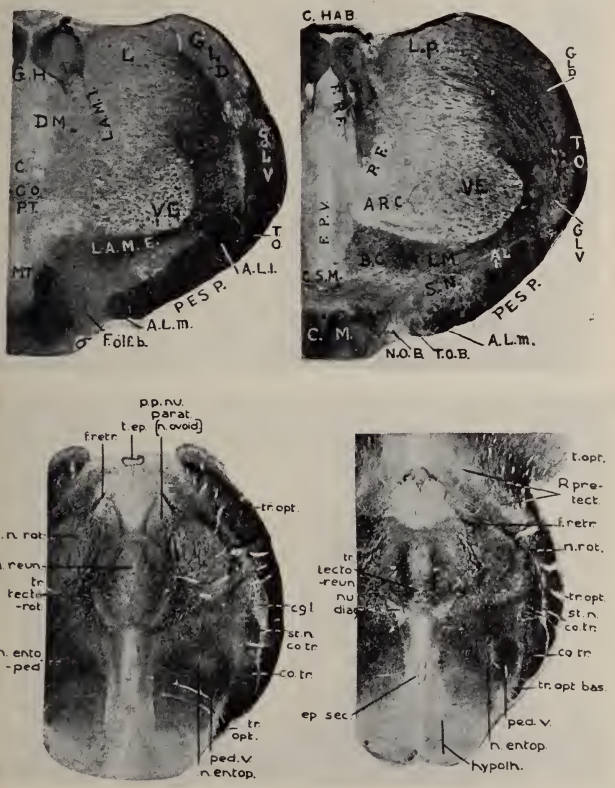

FIG. 2. Transverse section of the medial division of the diencephalon of Varanus salvator. f.periv. = fibrae periventriculares; f.retr. = fasc. retroflexus; g.h. = ganglia habenulae; n.diag. = nucl. diagonalis of Huber and Crosby (= nucl. magnocellularis tegmenti Frederikse); n.param. (reun) = nucl. paramedialis, which in the crocodiles joins the contralateral nucleus to form Edinger's nucl. reuniens); n.parat. = nucl. parataenialis (= nucl. dorso-lateralis anterior of Huber and Crosby); n.parvocell.ant. (nucl. dorsomedialis anterior of Huber and Crosby) = nucl. parvocellularis anterior* of the mammalian thalamus; n.rot. = nucl. rotundus; T.ped.v. = tractus peduncularis ventralis; tr.th.str. = tr. thalamo-striatalis (or pedunculus dorsalis thalami) = pedunc. thalami inferior anterior of the mammalian thalamus.

being turned to the ventricle; both receive fascicles from a system of poorly myelinated fibers that originates in the septum and runs medially to the fornix, ending partly in this reptilian dorsomedial anterior nucleus or its mammalian homologue, partly farther down in the hypothalamus. In the latter part of its course, the system appears to be increased by fibers arising from the nucleus. The relative size of this nucleus, compared to that of the remaining thalamus, is far greater in reptiles, especially in crocodiles (fig. 1), than in mammals (fig. 3), where it is surpassed by the large neocortical nuclei.

The large-celled *dorso-lateral anterior nucleus* of reptiles is clearly a homologue of the *parataenial nucleus* of mammals. In both groups these nuclei are located immediately against and underneath the taenia thalami (figs. 1, 2 and 3), and, in both, give rise to ascending fibers that end in the neostriatum, i.e., in the outer part of the reptilian striatum (in these animals not yet divided by an internal capsule into a nucleus lentiformis and a nucleus caudatus).

In mammals these fibers form part of the anterior inferior thalamic peduncle[1], in reptiles part of the so-called dorsal striatal peduncle.

Caudally the parataenial nucleus of reptiles extends in a medial direction, thus restricting the size of the parvocellular anterior nucleus. Dorso-medially to nucleus rotundus, it seems to form a separate group that may be homologous to the nucleus ovoidalis[2], first described in birds by Craigie and Huber and Crosby. Medio-ventrally it borders upon the *nucleus paramedialis* or *subrotundus*. This is especially evident in turtles (Dammonia, Testudo graeca).

The parataenial nucleus of reptiles continues also for some distance laterally over the nucleus rotundus, so that the frontal pole of nucleus rotundus is enclosed in the caudal extensions of the parataenial cell group.

In connection with establishing the homology of the dorso-lateral anterior nucleus of reptiles with the parataenial nucleus of mammals[3], it may be recalled that Nissl, who in his study on the thalamic centers of the rabbit ('13, p. 939) called this nucleus "medialer vorderer dorsaler Kern", found it intact after cortical extirpation. This is confirmed by J. Droogleever Fortuyn's observation (l.c. p. 41), that cell degeneration in this nucleus was especially evident in those of his rabbits in which the neostriatum had also been damaged. Besides, in the crocodile as well as in Vespertilio murinus, we could trace tectal fibers ending in this nucleus. An additional argument for homologizing the nucleus dorsolateralis anterior of reptiles with the parataenial nucleus of mammals is that both the dorso-lateral anterior nucleus and the parataenial nucleus are characterized

[1] Probably these fibers from the parataenial nucleus to the striatum led E. Sachs, the nephew of our jubilaris, to accept the presence of striatal projection fibers from the mammalian anterior nuclei. This peduncle is called "dorsal" in reptiles in contradistinction to the ventral striatal peduncle, which contains the descending fibers arising from the paleostriatum (or globus pallidus).

[2] Not to be confused with the nucleus ovalis (Bellonci's nucleus), nor with Rioch's nucleus ovoides, a midline nucleus in mammals.

[3] As may be expected, this nucleus is especially evident in lower mammals, Didelphys (Chu, '32), Armadillo (Papez, '32); rat (Gurdjian, '27), Xantharpyia (Suzuki, '36), dog and cat (Rioch, '29 and Ingram, Hannett and Ranson '32). In Primates it has a much smaller relative size (Vogt, '09, Friedemann, '12, Le Gros Clark, '30).

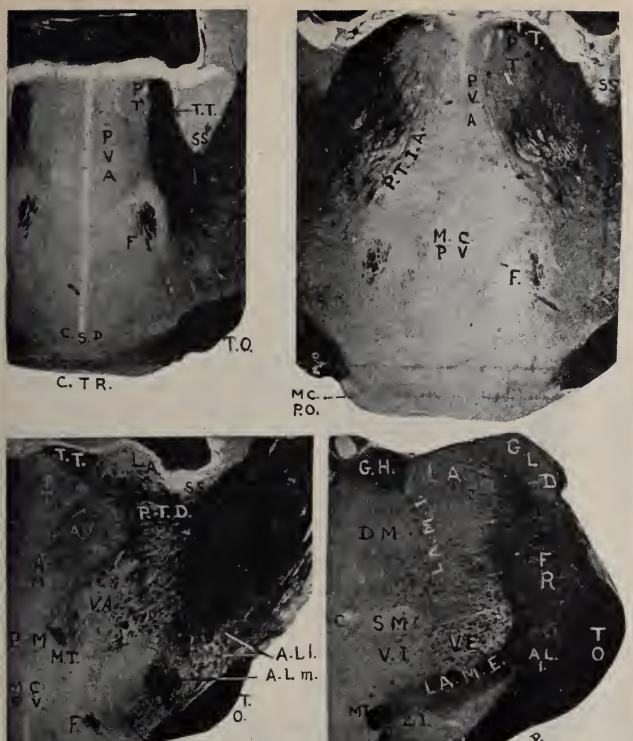

FIG. 3. Diencephalon of Xantharpyia amplexicaudata, after N. Suzuki. A.D. = nucl. antero-dorsalis; A.L.L. and A.L.M. = ansa lenticularis lateralis et medialis; A.M. = nucl. antero-medialis; A.V. = nucl. antero-ventralis; Arc. = nucl. arcuatus; B.C. = thalamic fibres of the brachium conjunctivum cerebelli; C = nucl. centralis; C.hab. = comm. habenularum; C.M. = corpus mammillare; C.S.D. = comm. supramammillaris; C.TR. = comm. transversa (Gudden; s.com.supraoptica ventralis) Co.P.T. = comm. principalis thalami; D.M. = nucl. dorso-medialis; F. = Fornix; f.F. = fasc. of Forel; F.olf.b. = fasc. olfactorius basalis (Wallenberg); F.P.V. = fibrae paraventricularis; F.R. = formatio reticularis; F.R.T. = fasc. retroflexus; G.H. = gangl. habenulae; G.L.D. = gangl. geniculatum laterale dorsale; G.L.V. = gangl. geniculatum laterale ventrale; L. = nucl. lateralis; L.A. = nucl. lateralis anterior; L.M. = lemniscus medialis; L.P. = nucl. lateralis posterior; LA.M.E. = lamina medullaris externa; LA.M.I. = lamina medullaris interna; M.C.P.O. = nucl. magnocellularis postopticus; M.C.P.V. = nucl. magnocellularis paraventricularis; M.T. = tr. mammillo-thalamicus (Vicq d'Azyr); N.O.B. = nucl. opticus basalis (= gangl. ectomammillare Edinger); P.F. = nucl. parafascicularis; P.M. = nucl. paramedialis; P.T. = nucl. parataenialis; P.T.D. = pedunculus thalami dorsalis; P.T.I.A. = pedunculus thalami inferior anterior; Pes p. = pes pedunculi; S.M. = nucl. submedius (= nucl. ventro-medialis); S.N. = substantia nigra; S.S. = stria semicircularis sive stria terminalis; T.O. = tr. opticus; T.O.B. = tr. opticus basalis; T.T. = taenia thalami; V.A. = nucl. ventralis anterior; V.E. = nucl. ventralis externus; V.E.p. = nucl. ventralis externus pars posterior; V.I. = nucl. ventralis internus; Z.I. = zona incerta.

by large cells and a conspicuous blood supply. Finally the fact that the dorso-lateral anterior nucleus of reptiles borders medio-caudally upon a paramedial (subrotundus) nucleus agrees with the observations of d'Hollander, Miura and J. Droogleever Fortuyn that the parataenial nucleus of the rabbit borders ventro-caudally upon the paramedial nucleus of this animal (Nissl's medialer vorderer ventraler Kern).

The *nucleus rotundus* of reptiles lies underneath the oral course of the fasciculus retroflexus, which then passes latero-caudally along this nucleus. Caudally, the nucleus rotundus flattens out laterally. Thus flattened it diminishes gradually and extends underneath the pretectal nuclei until the level of the posterior commissure of the midbrain. At its caudal levels, the lateral part of the nucleus is more and more occupied, and finally replaced, by fibers of the tectothalamic tract, a bundle first described in birds by Edinger and in reptiles by Huber and Crosby and Shanklin. This tract, arising from the caudo-lateral part of the mesencephalon at the junction of the tectum and torus semicircularis, sends fibers into the nucleus rotundus as well as into the parataenial nucleus. Somewhat finer fibers of caudal origin, probably arising in the nuclei commissurae transversalis, join the ventral side of the coarse-fibered tecto-thalamic tract and seem to end in the subrotundus or paramedial nucleus and, in crocodiles, in its confluence, the nucleus reuniens. As stated above, the *paramedial or subrotundus nucleus* varies considerably in reptiles. It is paired in serpents and lizards, but in Dammonia (a turtle) the nuclei of both sides join to form a midline nucleus, which, in the alligator and crocodiles, grows out to the *nucleus reuniens* of Edinger. The junction of these nuclei into a midline nucleus goes hand in hand with the appearance of a decussation of their caudal afferent fibers, which, in these animals, apparently end in the opposite as well as in the homolateral nuclear gray[4].

Close to the ventricular wall, underneath this nucleus, lies a triangular group of very large cells, described by Frederikse as nucleus *magnocellularis tegmenti*. Thinning out laterally, this group of cells forms the lower limit of the dorsal thalamus. As this nucleus increases caudally in the mesencephalon, we consider it rather a tegmental mesencephalic than a thalamic constituent. It seems to be homologous with Huber and Crosby's diagonal nucleus and forms a valuable "point de repère."

Although the reptilian and mammalian homologies of the nucleus parvocellularis anterior and nucleus parataenialis in my opinion leave little room for doubt, it is far more difficult to ascertain the mammalian homologue of the *nucleus rotundus* of reptiles.

First of all consideration must be given to the possibility that the nucleus rotundus of reptiles may be included in the caudal portion of the mammalian parataenial nucleus, in which Rioch distinguished two parts, an oral part with large cells less densely arranged and a larger part more closely packed. This distinction seems possible also in Xantharpyia where the caudal division is conspicuous because of its rounded outline. Considering the close relationship be-

[4] Although the afferent system to this nucleus is quite conspicuous, we have not been able to trace its efferent fibers.

tween the nucleus dorso-lateralis anterior or parataenialis of reptiles and the nucleus rotundus of these animals, this possibility should be at least kept in mind, the more so as in Vespertilio murinus the caudal part of the nucleus parataenialis is connected with the tectum and this connection might as well represent the tecto-parataenial as the tecto-rotundus bundle of reptiles. There is, however, also the possibility, advocated by Le Gros Clark, that the reptilian rotundus is represented in mammals by a nucleus of a very different topography. In this connection it may be emphasized that the nucleus rotundus of reptiles lies dorso-laterally to the paramedial nucleus and its confluence, the nucleus reuniens. This topography holds good also for the nucleus submedius of mammals (Le Gros Clark's ventromedial nucleus).

The fact that the nucleus submedius of mammals has a far more caudal and ventral position in the thalamic complex than the nucleus rotundus of reptiles is not necessarily an argument against this comparison since the whole triad of the mammalian anterior nuclei—the antero-dorsal, antero-ventral and antero-medial cell groups, which is connected with the bundle of Vicq d'Azyr and projects on the cingulate cortex (Le Gros Clark, J. Droogleever Fortuyn), is lacking in reptiles, where neither these nuclei nor a cingulate cortex occur. This mammalian triad, however, lies immediately behind the parataenial nucleus of mammals, wedging in between the latter and the rest of the thalamus. The ventral displacement of the mammalian ventro-medial nucleus in comparison with the reptilian nucleus rotundus may be enhanced by the development of two other mammalian cell groups not occurring in reptiles: the dorso-medial and anterior ventral nuclei.

The homology of the reptilian nucleus rotundus with the mammalian ventro-medial nucleus may be supported by the fact that Nissl in his decortication experiments found few changes in this region.

As stated before, the caudo-lateral part of the reptilian nucleus rotundus contains the fibers of the tecto-thalamic tract. These form a sort of lamina medullaris in this part of the reptilian thalamus. In connection herewith it is interesting to notice that, according to Le Gros Clark, tecto-thalamic fibers occur in the mammalian lamina medullaris interna which lies laterally to and underneath the triad of anterior nuclei.

Another argument in favour of a homology of the reptilian nucleus rotundus with the mammalian ventro-median nucleus or nucleus submedius is afforded by Le Gros Clark's statement that the latter nucleus has also striatal connections. The difficulty, however, lies in the fact that the ventro-medial nucleus or nucleus submedius is not always distinct or, at least, not always distinguished in the literature on mammalian thalamic nuclei, from the nucleus ventralis internus, a cell group lying ventro-laterally to the nucleus submedius. Bodian traced fibers from the latter nucleus to the inferior thalamic peduncle, which contains neostriatal projections. Morrison confirmed its non-cortical character for the dog, finding no degenerations whatever in this nucleus after decortication. In Papez's semi-decorticated dog, only a connection with the amygdala was found.

An additional argument for the homology of the nucleus rotundus with the

ventro-medial cell group may be seen in Papez's and Bodian's demonstrations of tectal fibers ending in the median part of the ventral nucleus (as well as in the reuniens nucleus). These fibers apparently form a part of Glorieux' *commissura principalis thalami*, which thus probably corresponds to the large thalamic commissure of crocodiles. In favor of the homologizing of the nucleus rotundus with the ventro-medial nucleus or nucleus submedius, is the fact that the fasciculus retroflexus descends immediately behind it as it does behind the nucleus rotundus of reptiles. Granting the strength of these arguments, the principal argument which may be advanced against this homology lies in the fact that the nucleus submedius or ventro-medial nucleus is a rather variable feature of the mammalian thalamus. It is very conspicuous in Macrochiroptera (Le Gros Clark, Suzuki) and quite evident also in Talpa, rodents and Carnivora. In the Microchiroptera, however, we have not been able to distinguish a nucleus that, in its topographic relations, resembles the conspicuous nucleus submedius of the Macrochiroptera[5].

Among the many midline nuclei present in the mammalian thalamus, the most probable homologue of the reptilian (especially crocodilian) nucleus reuniens seems to be the nucleus centralis medialis of recent authors (cc. of Nissl l.c. fig. 13 to 17), which, according to Nissl, has no cortical connection, although Bodian traced striatal fibers from it. Its paired frontal continuation, the *nucleus paramedialis* of d'Hollander and J. Droogleever Fortuyn (medialer vorderer ventraler Kern of Nissl) resembles the frontal paramedial continuation (in some reptiles the only representative) of the nucleus reuniens.

As stated before, in the crocodiles the caudal part of Edinger's nucleus reuniens contains a large number of crossing afferent fibers of caudal origin. This decussation might be called *commissura principalis thalami*. In mammals, a similar system of crossing fibers has been described by Glorieux at the corresponding level behind the central nucleus. According to Glorieux these crossing fibers arise from the medial geniculate nucleus. A real medial geniculate nucleus is not present in reptiles. Only the subgeniculate (geniculate C or nucleus of the commissura transversa) is found here. Since, however, the real medial geniculate (the origin of the acoustic cortical projection) develops in connection with the mammalian subgeniculate, the fibers described by Glorieux may well correspond with the caudal afferent tract of reptiles.

The homology of the reptilian reuniens with the mammalian central nucleus is proved by the fact that Le Gros Clark as well as J. Droogleever Fortuyn showed that this nucleus has no cortical connections at all. Bodian traced striatal connections from this nucleus.

[5] However, in Vespertilio murinus, a nucleus closely resembling the nucleus rotundus is found at a far more frontal level, underneath the parataenial nucleus. This nucleus is also intercalated in neostriatal fibers and its position resembles topographically that of the avian nucleus rotundus. Further researches may throw more light on this cell group and in general on the question of the mammalian homologue of the reptilian and avian nucleus rotundus.

As stated before, below and behind the crocodilian nucleus reuniens, lies the Huber and Crosby large-celled diagonal nucleus, Frederikse's nucleus magnocellularis tegmenti, which probably should not be considered as belonging to the dorsal thalamus, but to the ventral thalamus and which extends farther back in the tegmentum mesencephali. The topographic relations of the mammalian homologue of this nucleus also plead for the homologies stâted above, for this nucleus apparently is represented by Grünthal's nucleus paramedianus[6] in the dog's brain (Grünthal l. c. cell group 6). Rioch applied the same name to this nucleus in his 1931 article (fig. 6 and 7). This homology is confirmed by the fact advanced by Rioch (l.c.p. 379) that the mammalian paramedianus (just as the reptilian diagonalis or magnocellularis tegmenti) continues into the tegmentum of the mesencephalon. Rioch also pointed to the numerous fine periventricular fibres gathering underneath this nucleus as a feature which also holds good for the reptilian nucleus in question. In both groups these fibers form the periventricular system of Schütz, arising in the hypothalamus and ascending behind the commissura principalis thalami to the periventricular gray of the aqueduct (cf. fig. 1 and 3).—

It lies outside the scope of this paper to discuss the other projection nuclei of the dorsal thalamus. Since these other nuclei are concerned chiefly with neocortical projections, it is quite understandable that they are absent or hardly indicated in Reptilia.

CONCLUSIONS

Comparative studies of the reptilian and lower mammalian thalamus render it probable that the reptilian nuclei dorso-medialis anterior and dorso-lateralis anterior of Huber and Crosby correspond to the mammalian nucleus parvocellular anterior* and parataenial nucleus respectively. The reptilian nucleus reuniens and its paired frontal continuation, the subrotundus or paramedialis, is homologous to Nissl's central nucleus and d'Hollander's nucleus paramedialis respectively. The nucleus rotundus of reptiles may be represented by the nucleus submedius of mammals.[7]

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[6] This nucleus should not be confused with the above mentioned *nucleus paramedialis*, which occupies a much more frontal level.

[7] Many thanks are due to Dr. Elizabeth C. Crosby for her generous contribution of time in editing this article.—Ed.

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AGE AND REORGANIZATION OF CENTRAL NERVOUS SYSTEM*

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INTRODUCTION

". . . It is a matter of fact that the symptoms of such intra-uterine cerebral defects (motor pareses) are not always manifest at birth, and indeed a number of months may pass before it becomes evident to the physician that the child's cerebral condition is not a normal one. A very fair percentage of cases which appear to begin during the first years of life could properly enough be classified among the prenatal palsies, and if in any child the first symptoms of a cerebral palsy are noticed several months after birth, and yet the period of labor was entirely normal, I should be inclined to classify that case rather among the prenatal palsies than among the birth palsies.

"The birth palsies begin naturally enough with the period of labor. The history in these cases clearly shows that the labor was either excessively prolonged, or that an instrumental delivery was resorted to, in which case the brain has evidently suffered mechanical injury. Premature delivery is responsible for many cerebral palsies; but the symptoms may not be fully developed until months after birth." (31.)

Written by Dr. Bernard Sachs in 1895 these paragraphs illustrate the chief difference between the reaction to injury of the central nervous system in the infant and adult, namely that lesions sustained in infancy may cause little or no immediate effect although pronounced symptoms may develop later in life. A second difference is that injury to the central nervous system must be larger in the infant than in the adult to produce a corresponding deficit. This paper will review the evidence that these two striking dissimilarities between adult and infant are due to the greater capacity of reorganization within the central nervous system of the infant.

PREVIOUS LITERATURE

The clinical evidence that the reactions of the central nervous system of the infant differ from those of the adult has become too well known in this century to need more than passing mention. The palsy which follows birth injury or congenital abnormality in the human infant has been described many times since the original article of Little (27) and those of Freud (9, 10), Osler (30), and McNutt (29). The material has been more recently reviewed by Ford (7, 8), and by Collier (3, 4).

The motor manifestations of cortical injury in infants are either paresis, epilepsy or involuntary dysrhythmias such as chorea. Any one of these disorders may appear in the first days or weeks of life but most often it is not obvious until the second half of the first year of life at the earliest and often not until much later. When the symptoms appear early they are always severe and there is usually some evidence of extensive and generalized cerebral damage often accompanied by grave mental deficiency or idiocy.

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When the symptoms appear later they are usually more focal and manifest themselves at the age when more complex motor performance, such as walking or the finer prehension of the fingers, is normally begun. In such cases many of which have been under observation from the time of birth by competently trained individuals, the early motor performance has been thought entirely normal. But at a later age many of these same children exhibit serious abnormalities of posture and movement. In a few instances psychological or behavioral tests have been more sensitive than the less specific examinations during the early months (5). Thompson (32) has reported two cases of cerebral abnormalities which at the age of six months showed definite defects in motor prehension although other localizing signs were negative at the time. It is probable that more widespread use of such tests in the future may be valuable for early detection of minimal localizing signs in infants which later exhibit indications of more serious damage to the cerebral cortex.

There is likewise clinical evidence that cerebral insult in the infant has less ultimate effect than in the adult. The severe cerebral palsies have widespread injury to the brain. But there are many other cases reported wherein the cortical injury at operation or autopsy was much greater than had been expected from the symptoms. The extent of porencephalies, in particular, is often unsuspected during life because of lack of localizing signs.

Experimental evidence fits well with the clinical material. The earliest observation seems to be that of Vulpian who in 1866 (35) writes:

"When one attempts an experiment of this sort [hemidecortication] on mammals it is necessary whenever possible to make use of very young animals; for on the one hand, these support operation well and on the other, the functional relations between the different parts of the encephalon are not yet as narrowly circumscribed as they later become; to such effect that ablation from the brain has less influence on the action of other parts than in the adult animals."[1]

Other functions which are integrated through the central nervous system have the same increased capacity for restitution of function in the young. Beach (1) reported that changes in the maternal behavior of the rat are directly dependent on the amount of cortical tissue removed at operation, but that during maturity those rats operated upon in infancy behave more nearly like the normal than do animals from which an equal portion of cortical tissue has been removed at a later age. Tsang (33, 34) finds the same difference in ability to learn mazes between rats operated on in infancy and during maturity.

Kabat (17) has reported similar differences in connection with another type of function of the central nervous system. His experiments show that young puppies have greater resistance to asphyxia or arrest of brain circulation than do dogs. It is thus possible that both respiratory function and the more complex voluntary and conditioned responses are influenced as Vulpian suggests by the fact that various areas of central nervous system are less well differentiated in the young.

Another factor which may alter the reactions of the infant is stressed by Himwich and his co-workers (12, 13, 14, 16), namely, that in rat, cat and dog the various portions of the nervous system of young animals require less oxygen than do those of the adult; and that, furthermore, young tissue maintains electrical reactions longer than does the old under conditions of cerebral anemia. Thus, if the heart is suddenly excised, cerebral electrical activity persists longer in the infant than in the adult. This difference disappears during the period of early growth.

During the past six years a series of experiments has been conducted in this Laboratory which has been designed to further elucidate the difference conferred by age on the reactions of the central nervous system of the primate. The detail of much of this work has already been published (18, 19, 20, 21, 22). It will here be summarized together with more recent material.

[1] Translated by authors.

METHOD

A comparison of motor performance has been made before and after ablations from the central nervous system in both adult and infant monkeys and chimpanzees. The greatest number of observations has been on rhesus (*Macaca mulatta*). The infants, born in the Laboratory colony, were operated upon usually during the fourth week of life. Fully mature monkeys were operated upon by the same procedures and under the same conditions of time interval between operations, etc. Many other young or adolescent animals of various ages have also been used for comparison.

OBSERVATIONS

Motor development of the normal infant. Figures 1 and 2 illustrate the various stages in the normal motor development of the infant macaque during the first

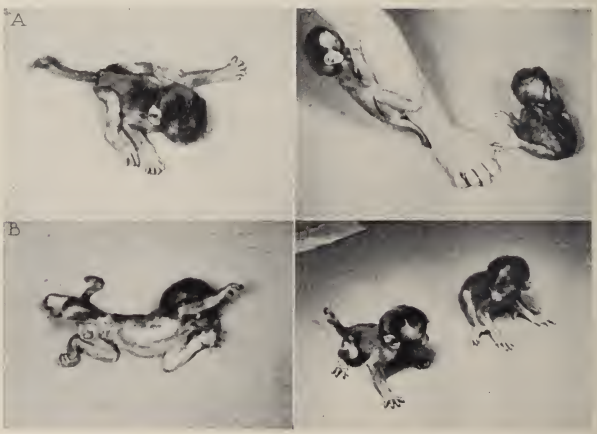

FIG. 1. Motor status of infant *Macaca mulatta* during first 2 weeks of life: A and B, 1st day; unable to raise head or right; C reflex grasping and posture at end of first week; D, posture at end of second week.

six months of life. A monkey of this species matures during the fifth year of life, but its motor status at the end of the first six months is usually about as complex as it will become. During the first week it can usually right itself but fails to raise the belly from the floor (fig. 1). Its efforts at rhythmic progression are ill-coördinated and without success. Reflex grasping is, however, strong and constant, and the sucking reflex is almost as intense. During the first month the infant becomes able to sit and crawl in a widespread and badly executed sprawl, and clinging continues. During the second month (fig. 2) voluntary prehension first appears but it is not until about the fourth to sixth month that these infants will reach for food, grasp it and bring it to the mouth. The more usual manner at this stage is to bring the face down to the food, a

habit entirely lost by all normal older monkeys. Fine prehension and balance in jumping and running develop last.

Effect of ablations from the motor cortex. It is possible by appropriate cortical ablations in older monkeys to reproduce the various stages of motor performance seen in the normal development of the infant. Figure 3 shows such stages in the recovery of voluntary motor power which appear after bilateral ablations from the motor cortex. If figures 2 and 3 are compared the striking similarities in the development of motor performance can be seen. The monkey in figure 3 was operated upon during the second six months of its life (22). Its preoperative performance at this time was as complex as that of an adult. After opera-

FIG. 2. Stages in motor development of infant *Macaca mulatta:* A, failure to "place" right foot, first week; B, posture of one week old infant (lt) compared with that of four week old infant (rt); C, feeding without use of hands, third month; D, adult method of feeding, fifth month.

tion all voluntary power was at first lost and it was unable to stand or right itself. Reflex grasping was intense, but voluntary grasp was absent. A week later, righting to the prone position became possible and still later, standing and progress as well. Finally, feeding was carried out but by the method of the infant, bringing face to food on floor without the use of the hands. Posture became likewise more nearly normal.

It is known that in older monkeys the motor areas of the cerebral cortex, areas 4 and 6 of Brodmann, apparently integrate all voluntary or purposeful skilled movements (2, 11), for bilateral removal of these areas from the adult monkey or chimpanzee produces an animal totally devoid of voluntary move-

ment; one which executes only the reflex grasping and postural responses seen in the thalamic preparations of Magnus (28); and which differs little in total performance from the newborn infant.

It has likewise been shown that removal of these same areas 4 and 6 from the infant has almost no effect on motor performance at the time of operation. Immediately on recovery from ether anesthesia clinging and climbing are possible. There is, however, a slight change in posture and the extremities are more flaccid to passive manipulation than before operation. The immediate effects of removal of an entire frontal lobe or a hemisphere from a four-week infant are of this same order. There is slight loss of "tone" and slight change in posture for a few days or hours and then all focal signs disappear for a time

FIG. 3. Infantile type of motor performance following bilateral ablation of areas 4 and 6 in a six month old *Macaca mulatta:* A, before operation; B, one day after operation, inability to right; C, one week after operation; D, 2 months later. (Cf. fig. 2).

(fig. 4). Later, when motor performance becomes more complex, such animals exhibit paresis, although never to the degree seen in the adult.

Still later, from the sixth month on, spasticity appears but is never more than moderate in intensity. In adults, deprived of areas 4 and 6 spasticity appears and becomes maximal in a few days after operation.

One other factor intimately affects motor function following cortical ablation, in the young monkey to an even greater degree than in the old. When only a fraction of the sensorimotor cortex is removed at operation, the length of the interval before a second ablation has direct influence on final recovery of function (18). Thus simultaneous bilateral ablations always result in greater eventual deficit than seriatim ablations and longer intervals between operations are followed by greater recovery of function.

Because the capacity for motor performance of the animal operated upon in infancy was so much greater than that of the adult following the same procedure, ablations of motor areas were next carried out on a series of animals of intervening ages (22). It was found that severity of paresis increased gradually

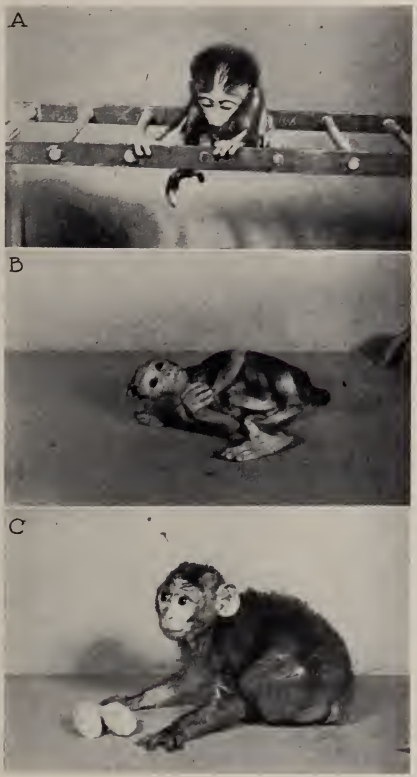

FIG. 4. Motor status of a 3 week old *Macaca mulatta:* A, before operation; B, one day after bilateral ablation of areas 4 and 6; C, the same animal 6 months later.

with age at operation over the first two years of life. But that only if the bilateral ablation of areas 4 and 6 were carried out during the first six months was recovery sufficient to enable the monkey to maintain its life under ordinary cage conditions. If operated on after the end of the second year no voluntary func-

tion returned, but the animal remained like a totally decorticate preparation for the rest of its life.

Extirpation of area 8, the motor field for conjugate deviation of the eyes and head, will produce in the infant almost as much effect as in an older animal. Deviation of the head and eyes in either case is toward the side of the lesion and lasts a matter of some days or weeks. There is a more evident immediate effect of removal of this area from the infant than of removal of any other single cortical area at the same age.

Effects of ablations from non-motor cortical areas. The non-motor areas can be divided into four groups: 1) the frontal association areas (areas 9–12 of Brodmann); 2) the occipital cortex concerned with vision; 3) the parietal areas which are a part of the sensorimotor cortex, but not primarily concerned with the effector motor system; and 4) the temporal lobe.

1) Complete removal of the frontal association areas from both hemispheres in the older monkey results in an increase in total activity which is characterized by easy distractibility and excitability but which is unaccompanied by any other change in motor performance (25). Removal of these areas in infancy causes no immediate visible change in the elementary motor performance, but with age a compulsive motor hyperactivity appears which cannot be distinguished from that of animals which have had the same areas removed when adolescent or mature.

Jacobsen (16) has reported that bifrontal ablations, whether performed in infancy or later, completely deprive the animals of the ability to "recall", *i.e.*, "immediate memory" is lost, and completely lost, when all of the frontal association areas have been removed either in infancy or later.

2) Total removal of the occipital lobes likewise results in total abolition of object vision whether the ablation has been made in infancy or later. This we have observed in two infant monkeys of our series and similar findings have also been reported by Tsang (34) in infant and adult rats. We have encountered no other record in the literature comparing the effect of quantitatively equal partial ablations from visual cortex of infant and adult.

3) The effects of parietal ablations on the adult monkey are known (23), but those which occur in the infant are more uncertain because of the difficulty in appraisal of sensory defect at this early age. In the older animals touch and proprioception are slightly but permanently impaired. Placing reactions disappear when the entire parietal area is removed. There is a change in motor performance as a result of this sensory defect. Posture is altered and the extremities are moved awkwardly because of loss of proprioception unless movement is carefully controlled by vision, but fine movements such as finger prehension may be accurately performed.

In the normal monkeys placing reactions and fine finger movements are absent in infancy and appraisal of sensorium is almost impossible under any conditions.

One infant allowed to grow, after parietal ablation, has shown persistent absence of placing reactions but no other demonstrable defect. It is still alive, the lesion, therefore, is still unverified.

4) There are as yet no observations on the effect of temporal lobe ablation in the infant.

Effect of combined lesion of different cortical areas. In the older monkeys, then, primary ablation of the motor areas 4, 6 and 8 from the cortex directly affect motor performance in a known and predictable amount according to the site of the lesion. In younger animals the effect of similar ablations is slight in every instance immediately after operation and later becomes only moderate in intensity. In both young and old removal of the non-motor areas has no direct effect on motor status although total performance may be altered secondarily by visual or sensory defects or by restless hyperactivity.

In the older animals combinations of these lesions cause a combination of signs and symptoms such as would be expected, but in the infants the results are otherwise. If, for instance, the frontal association areas are removed unilaterally or bilaterally from an adult either before, after or simultaneously with areas 4, 6 and 8, no added motor deficit can be detected as the result of removal of these association areas. The same is true of parietal and occipital lobes.

However, if, following bilateral removal of areas 4 and 6 in infancy, a young animal is allowed to grow until improvement in motor performance has ceased and then a frontal association area or postcentral gyrus is removed, a markedly increased deficit in motor performance appears. This paresis which is the result of removal of a non-motor area is found, furthermore, both in the contralateral and ipsilateral extremities. The indication therefore is that, when the motor areas are removed in infancy, there is a reorganization of the remaining non-motor cortex which then integrates both contralateral and ipsilateral motor performance to a degree which is far greater than in the normal cortex.

Effects of lesions of basal ganglia. The functions of the basal ganglia in monkeys and chimpanzees seem to be those of coordinating voluntary motor activity. Large lesions of these nuclei or smaller lesions when combined with cortical extirpations from the motor areas result in tremor or involuntary movement of a choreiform type. This has been demonstrated in a series of adolescent or adult animals (21), and observations on infants are now under way.

The immediate effects of combined cortical and caudate lesions in the infants have been striking, because no other lesion or combination of lesions has so severe an immediate effect on motor performance. In no instance has ablation confined to caudate or putamen, either unilateral or bilateral, produced any change in motor performance. But, combined lesions of caudate and area 6 have in the four cases in which this extirpation has been made, produced a marked immediate motor deficit, and a severe permanent effect. The animals have striking limitation of movement such that they move little for some days after operation. They are unable at first to suck sufficiently well to feed themselves from a nipple. They tend to hold their extremities tightly flexed and motionless and there is increased resistance to passive extension (21).

The three of these four animals which had *simultaneous* bilateral ablations have all had epileptic attacks for some days after the operation, so severe in two cases that they had to be controlled with amytal, and showing in electro-

encephalogram, typical *grand mal* seizures. *Petit mal* episodes were also found and a permanent and constant change in the electroencephalogram as well (24). Later these animals developed tremor and moderate paresis, as in the adult, but epilepsy disappeared.

DISCUSSION

From the observations of motor performance before and after cerebral cortical extirpations which have been briefly cited above various conclusions may now be drawn concerning the functions of the infant and adult central nervous systems. The differences between the two may be compared and speculations may be advanced as to the nature of the changes which convert the brain of the infant to that of the adult.

Cortical function in infancy. Since the motor performance of a new born infant monkey resembles that of an adult deprived of cerebral cortex, it is assumed that the cortex of the infant has little function during this period. But, although the pattern of movement of the infant is as limited as that of the thalamic adult, the performance of the former has greater variety in the use of this pattern and less stereotypy also. Decortication of an infant reduces spontaneous movement definitely, although reflex grasping, clinging and sucking remain present. Furthermore, some function is present in the cortex since at operation stimulation of area 4 produced movement in these animals. Hines and Boynton have reported this matter in some detail (15).

The same limited function of infant cortex is made evident by cortical ablations. Small lesions such as would produce well marked changes in an older animal cause no visible effect if made during the third or fourth week of life. Larger lesions such as unilateral removal of areas 4 and 6 or of one frontal lobe produce a slight deficit during the hours immediately after operation. But 48 hours later there is no disturbance of posture or movement. When an entire hemisphere is removed the immediate effects are even more noticeable. The extremities are held more extended than before operation, they move more slowly and the amount of spontaneous movement diminishes. It is several days before the affected limbs regain symmetry with the normal extremities.

Simultaneous bilateral removal of areas 4 and 6 from the infant has a more severe immediate effect. For several days after operation these infants fatigue easily. Resistance to passive manipulation disappears entirely. The change is so marked that the infant lies limply most of the time as shown in figure 4. Placed on a ladder immediately before operation this infant was able to cling and hold its head erect at this age. Immediately after operation it lay on whichever side it was placed, although reflex grasping and clinging were still strongly present. By the end of the first week it had recovered all of its preoperative skill. After this date movement became progressively more complex.

Area 8 must function before other cortical motor areas since its removal from the infant cortex produces marked deviation of the head and eyes at a time when other motor performance is only slightly affected by cortical ablations elsewhere in the motor areas.

Function of basal ganglia in infancy. The function of the infant basal ganglia

must be much like that of the adult. Large bilateral or unilateral lesions of caudate or putamen or both have no immediate visible effect on the motor status of the infant. Excision of the basal ganglia of the adult may result in slight tremor, but only when there is a large bilateral lesion. Bilaterality and lack of focal representation of function in these nuclei have been shown by excision in both age groups.

The basal ganglia of both adult and infant affect movement more severely, however, if area 6 of the cortex is removed together with either caudate or putamen. There is then an immediate change in posture and movement. In fact, the only infants with immediate and severe effects as the result of injury to cerebrum are those with this combined cortico-subcortical ablation. Paresis, epilepsy and dysrhythmias have all followed such lesions.

Electroencephalograms show similar results (24). During the first weeks of life there is little cortical electrical activity, but it increases gradually in amplitude and frequency during the first six months. Extirpations from the cortex during this time alter little the form of the electrical potentials from the remaining brain tissue. But combined extirpations from cortex and basal ganglia are followed by material changes in the form of the potentials.

Cortical function in the adult. The functional localization within the cortex of the adult monkey is, of course, specific and hence the results of ablations from any area are predictable. Recovery, or reorganization, following partial ablations is slight but always present. After total removal of areas 4 and 6 motor function never progresses beyond that of the newborn infant if the animal is adult at the time of operation. Growing monkeys between the ages of infancy and maturity show decreasing ability to develop or recover voluntary motor function. Appropriate cortical ablations at any age will immediately reproduce the infantile state as far as motor status is concerned.

The process of maturing of the central nervous system is thus shown to be one in which the adaptability of the cortex becomes less and certain areas of cortex become "set" to integrate certain functions which cannot then be integrated through other channels.

Nature of the difference between infant and adult cortex. That the difference between adult and infant restitution of motor function is a property of the cortex in great part at least has been shown above, for subsequent removal of "non-motor" cortical areas will increase motor deficit when motor areas have been removed in infancy. The basal ganglia on the other hand seem to function during infancy about as they do in the adult as far as present evidence goes.

Jacobsen, Taylor and Haslerud (16) have discussed the nature of the cortical process which is requisite for functional reorganization. They state that there are three possible processes whereby restitution of function might occur following cortical ablation: "1, The subject learns to adjust without the lost function; 2, Some other part of the nervous system not previously concerned with the activity vicariously assumes that function; 3, There is a dynamic reorganization within a partially destroyed system." They believe the latter to be the case, and it is certainly the most reasonable one to use if possible.

The first postulate, that the organism gets along without the function is,

in the present instance, impossible. Vicarious function may be that by which the frontal association areas 9–12 assume motor function as when areas 4 and 6 are removed in infancy; but there is no evidence at present that they function in this way under any other circumstances. On the other hand, there is no doubt that the sensorimotor cortex including all frontal and parietal lobes acts in some respects as one unit. There are Betz cells as far back as area 5 with axons ending in the cord. The cytological structure of areas 9–12 is like that of area 8 and not very different from area 6. The work of Dusser de Barenne and McCulloch (6) indicates that the functional structure of the entire cortex of *Macaca mulatta* lies in bands and that these have alternate excitatory and inhibitory functions. If these complex interrelations are sufficiently similar, the entire sensorimotor cortex may be considered one functional unit and the concept of vicarious assumption of unusual function is unnecessary. Reorganization within a partially destroyed system thus remains the most reasonable concept.

The functions of regulation of conjugation deviation of the eyes and head illustrate this possibility well in both adult and infant. There are two areas which, on removal, produce deviation of head and eyes toward the side of the lesion. Removal of either or both of these areas (area 8 of frontal cortex, and the angular gyrus) causes a change which is only transient. Removal of a hemisphere produces permanent deviation, although there are no other known areas of cortex which alone will affect eye movement. This might be taken to illustrate the "dynamic reorganization" of Jacobsen as might many other instances of recovery of function following partial removal of cortical areas.

There are in contrast two functions of the cortex which we know to be totally destroyed by ablation both in the infant and in the adult. Vision is as completely and permanently altered by bilateral ablation of the occipital lobes of the infant as of the adult; complete removal of areas 9–12 also produces in both infant and adult, an animal incapable of immediate memory and one which is intensely and abnormally hyperactive. It may be assumed in these instances that all of the systems necessary for these functions have been destroyed and that there is no vicarious assumption of function.

The ability of the infant cortex to reorganize better than the adult remains to be explained. Within the sensorimotor system the reorganization may be either functional or anatomical. Since it is known that learning is easier in the young, this may account for the more complete motor pattern of the animal operated on in infancy although no fundamental understanding of the process is acquired by designating it as "learning." The fact that the young animals pass rapidly through a stage of partial paresis immediately following operation, whereas it takes many times longer to cover the same stages in the adult makes functional reorganization likely as anatomical changes do not occur as rapidly.

On the other hand, the process of recovery in older monkeys takes many months and it is possible to imagine in a system such as that of the infant when myelinization and proliferation of dendrites is not complete, that anatomical reconnections are possible within a system of complex interconnections. Thus

neurons which ordinarily integrated reflex arcs via the motor cortex might, by proliferation of dendrites, connect with neurones farther rostral or caudal in the absence of the motor areas. It is even possible to imagine that the process of neurobiotaxis might be here involved.

CONCLUSIONS

1. In monkeys and chimpanzees the factor of age affects directly the amount of recovery of motor function which follows ablations of the motor areas of the cortex.

2. Other areas of cortex reorganize to some degree to integrate motor function in the absence of the motor areas, at any age.

3. There is little restitution of function if operations are made after the second year of life, and only during the first six months of life is it sufficient to produce function adequate for the existence of the animal.

4. The basal ganglia function at birth and continue to show similar function throughout life.

5. After removal of the frontal association areas, 9–12, and the occipital areas, the remaining cortex shows no such capacity for reorganization of motor function.

6. The sensorimotor cortex may therefore be considered as a unit within which there is much less specificity of function in the infant than in the adult.

7. The capacity for reorganization in the absence of specificity may be considered at the present time as due either to functional or anatomical changes.

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THE INTER-RELATIONSHIP OF MIND AND BODY[1]

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When we climb in the high places of the earth, plodding slowly at mountaineer's pace with crampons on our boots, that we may keep foothold on the blue ice, we should stop from time to time and, steadying ourselves with our ice-axe for a moment, raise our eyes, weary with guiding our steps between crevasses, to the great peaks we would conquer, and see, too, the foot hills we have left behind. Only by gazing thus can the Alpine climber find values, and often he catches too, just then, a glimpse of beauty. So it is profitable to turn from our work in laboratories and among the sick, to survey the general state of our knowledge in larger sweep. We cannot hope to have added by our deliberations today anything of solving value in this ultimate problem. But we clarify to ourselves the state of our small knowledge, and, though we may throw on these matters no more light than that which Milton tells us shines in Hell, "enough to make darkness visible," yet it were well done.

The world has not yet made up its mind whether Plato or Aristotle was right—whether man is really Spirit or Machine. We here, probably, call him a transformer of power and straddle the question. It is quite certain, however, that without a good brain you cannot have a good mind, and good breeding begets good brain. But it is not enough for us to think of brain only. We must consider also the relation of the nervous system to the detailed and specialized activities of the rest of the body. It affects and is affected by the whole organism; and consciousness is found not as the resident of parochial places, but as the emergent distillate of the total structure. Neurologists have erred in being rigidly deterministic in their consideration of neural integration, and psychologists of some modern schools are not less vicious in their unbending and oversimplified dogmas regarding functional abstractions, existing, they would seem to want us to believe, in their own right. We see then, science, yearning to systematize and make rigid, ideas and theories: theories which to attain a goal, like runners in a hundred-yard dash, must be put between tapes.

In the early study of any knowledge, dogma and rigidity are needed;—the axioms of arithmetic and Euclidean geometry are required for simple living and for searching in an environment simply considered; but these hypotheses must become almost progressively more flexible if they are to be useful at all in any cosmic fashion; only buoyant variables can stay afloat in a solution of relativity!

We must know in order to appraise man's projecting power, that we are three dimensional, and we should have a lively suspicion that, in a space-time continuum, we may be four.

It may well be that the scientists' view of the Universe as being, as it were, mindless, non-creative, traditional, and lacking aim or object—"a bloodless dance of categories"—comes from some scientists' mistaking the discovery of a

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regulating Natural Law for a revelation of the Universe itself. To attempt to apprehend the stars in terms of a mathematical formula, or a Law of Gravitation, is probably like mistaking his electro-encephalogram or his brain metabolism for the personality of a poet.

Advances in knowledge come often, not by the addition of new facts but by a novel rearrangement of known material, giving new direction through a mental "jump", placing old knowledge on a new, a more manageable and more illuminated level. The Masters have all done this lifting. Copernicus, Newton, Darwin, Freud, Einstein: they have made patterns and order where there seemed disorder without aim; and when they have discovered the Design, whether in Cosmos, in Nature fixed or vital, or in Man, the organized whole is always found to be greater and more variable than the sum of its parts.

Correlation calls for definition of terms. But there is trouble here; for any set of phenomena may properly be described in exact technical terms in many manners. We may view epilepsy as a brain water-logged, or as a brain rhythm, or as a personality reaction; or, for that matter, the passion of love as a very short wave length indeed, or as phosphate of lime. No one aspect can tell everything, but all, could we find them, may. We must strive to inter-relate ideas, with as little technicality as possible; to find harmonious union in kaleidoscopic variety. The accuracy and authority of each science has to be taken for granted by every other science, yet no one science can explain all. Each profession begins as a conspiracy against the public, and the first defence of a new science against other sciences is to throw around itself breast-works of new names, not always for new ideas. No one technical observer can see how the war is going on, any more than can a company commander, blinkered, from his own section of trench. And should we succeed in fusing or integrating such varied facts as we have been regarding here, what we shall then see, or what we shall then know, may be something as unsurmised, as astonishing, and as vastly different from the factual material we have been trying to know, as oxygen and hydrogen are different from both light or heavy water. So each subject, here presented, can be but one facet of a vastly complex crystal.

Modern psychology,—despite strong grasp and vigorous reach, has regarded man as an entity, more or less isolated from the universal forces which made him, and are around him. And an entity over-simplified and stereotyped,—a cliff of obsidian beaten by the waves of social and biological environment. Over-symbolized and dogmatic, it has been technically concerned with man as a vital being without regard to the endless variety of that being and the endless variety of his reactions; and with little regard for the nature and variety of the patterned structure of his nervous system and the rest of his body; a structure enormously varied which necessarily permits and emits enormous variety of process and expression. Formerly structure was structure and force was force. And none doubted the antithesis of the two elements out of which the universe seemed to be composed. There thus grew a clear and obvious dichotomy of body and mind. However, matter, structure, substance, when the search into their nature grew fierce enough, eluded the materialists, and, changing its shape and attributes like witch and princess in the fairy tale, is seen to be force in different forms,

utterly without substance and impalpable. Even the notion of space-empty or space-ethereal has today been abandoned and all is viewed as activity, energy, force. Energy in cosmos has the power to turn into or to precipitate mass; function in living beings turns into or precipitates structure; the type and complexity of structure depends on the type and power of directive activity of the trapped fragment of driving power. The kind of structure then fabricated will determine the end-character and expression of the energy mediated through it. Nature, thus, is but energy,—patterned into worlds, patterned variously also for every stick, stone or bit of life upon them. We thus become one with our environment which pervades us wholly and into which we extend ourselves hugely. We hold our unique pattern as a momentary opportunity for experience on a radiant stream of creative continuity, designed for aim. We are coagula, innate with purpose in a flow of power,—and about to be dispersed! It is this unique dynamic pattern of energy imprisoned and constructed for so little a time that by varied procedures we have been here exploring.

Plotinus said that sensations are obscure thoughts, and intelligible or spiritual thoughts are clear sensations. Man has the power by the percipience of his senses to fabricate mental images. These, retained, recalled, and enlarged by imaginative interaction, he can then project into circumambient nature and so interefere with routine happenings both there and within himself. He can modify natural tradition, and, by creating new self-enjoying principles, he can recreate novelties for the future. There seems to be no end in him to the evolution, out of primitive homogeneity, of power upon power, of faculty upon faculty, through the ages. Great need in organism grows organic and special function. The repeated "striving-use" of function, eons long, grows structure and channelled power, and power long used, is an unconscious emanation. Mass and energy thus become interchangeable,—but only perfectly so for the mathematical physicist, who, like the rest of us when using but one set of instruments, can perceive and manage but one aspect of the Whole. For Mass and Energy are the same,—with a difference.

But where Vitality anywhere exists, Aim is found. A primitive consciousness exists as "purpose" in every living cell, and organizes itself as structure; this primitive mind becomes specialized, layer upon layer, segment upon supersegment, into complicated reflexes, later more complicated instincts, and later, still more complex emotional tones and feelings, integrated and channelled for expression through thalamus and hypothalamus. Finally there has been added the neopallium, the new brain, more and more exquisitely integrated; a concatenation of such ordered representation and *swift* activity that through it, primitive power can appear even as the gift of critical discrimination. Slowly too, this power is distilled into a sense of spacial and temporal relationship. Up to the present point of evolutionary time, the highest product of this captured, specialized, focussed energy of cosmic origin is our self-awareness, self-direction, power of surmise and power of speculative imagination which almost denies the universe itself for boundary—all radiated, implemented,—and sometimes disturbed,—by emotion.

Purpose is mediated by protoplasm. Consciousness is an enormous ampli-

fication of early purpose as primitive as tropism. And it is raised to its highest power and focussed for its greatest good by the contrivance of symbolism, and imagery, and the invention of the tool of speech. The distillate of consciousness is thus focussed into self-awareness. This achievement is nothing but the flowering of the aim, drive and purpose, innate and part and parcel of every cell in our bodies; this is as truly a part of each cell as is its mere "skeleton" with which by our ingenuity and skill we have made our senses familiar. So, instead of the Animula, Blandula, Vagula of The Emperor Hadrian we find the "soul" a focussed and aspiring Purpose, implemented by feeling, each "soul" unlike every other, living but in a tick of time, and carved out of the Absolute.

However we differ in degree, we do not differ in kind, from Amphioxus, that lowly creature with a primitive vertebral column, and translucent. We, too, have a backbone and are often also sufficiently transparent! So in some matters we have not marched so far along our road of Destiny.

To reiterate then, we regard mass as precipitated power and believe that in organisms that are vital (and living things differ from unliving things only perhaps, by the geometrical structure of their molecules) function and urgent need precipitates and patterns structure; this in turn transmits energy, and at the same time ordains much of its character and final expression. And it must not be forgotten that through the study of viruses the line between life and non-life in terms of behavior becomes truly a very soft border. Indeed the consciousness of plants and trees primitively considered may be in quality of the same stuff as our own; the apparent difference between ours and theirs being dependent on different speed and timing and focus. The experiments of Bose on plants show their movements and manners purposeful when translated into space-time terms that we can understand. As levels of bodily function, for the most part unconscious, are represented and re-represented in the evolving nervous system, so there are analogous segmentations of mental life. (A pox here! On that ecclesiastical inheritance, a dualistic vocabulary!). These levels are many mansions, and, for the conservation of energy and the conservation of ourselves, we try to put as many of them as possible, just like any other dug-outs, below the level of consciousness. Much of our feeling and sensory perception should be classed as almost effortless idea-activity at one of the deepest mental strata. The development of yet another mental threshold allows us to economize by the development of habits and conditioned behavior. This lower physiological level of educated habit furnishes a speedier reaction to our fierce and provocative environment than can be given by the imagery of ideas. These are discriminative, associative, creative, and enable us to know that we know, and to be self-contemplative.

We can bend, however, these high faculties in directions to which they were probably not intended to be bent. High faculties are laid down in us by evolution and by heredity, they develop by the friction of experience, and we use them in a manner often improper! We think, for instance, that we are exceedingly rational beings. Rather, our higher intelligence is often prostituted in service in that, when possible, we use our higher intelligence to explain away our lower

happenings. However, it was only the other day that we began to give a clear motive—authority to our emotional trends and antique desires in the determination of conscious thought and action. But, in the first fine careless rapture of that discovery, modern novelists, psychologists and painters have pertinaciously urged on us the premature destruction of the values of Truth and Beauty and have tried "to project their own tastes upon the empty canvas of a valueless Universe." (Joad) Some still try to dethrone the majesty of man's Reason; to replace it, not augment it, by a catch-as-catch-can Subconscious. This is a revolt of the helots indeed—a mere kitchen rebellion—the puny gesturing of a generation that got tired out, and of its successor that was born fatigued. However, should the inherited ration of power prove puny in any one of us, and at long last, we find our distilled capacity for abstract thought humiliatingly small, our directive awareness, thank goodness! is always able to put that modicum, like Eve's dress, where it does the most good. Self-awareness makes for conservation of *self,* or of the changing complex called self. And in the midst of change, memory swiftly associates what are perhaps the molecular designs of old impressions of sense and thought, so insuring personal identity, and producing individual unity throughout a life-history of flexible variation. Memory is the thread of Ariadne in the labyrinth of ever changing personality, by grace of which we contrive to find our way back to the past and, by using the images of recalled experience, find our way also into the future.

Thus the evolution of stratified structure in the nervous system is essentially the precipitation of function always directional; at first primitive and homogeneous, later specialized into variety, and multiplied into complexity: the old always containing within itself the new, burgeoning through material impulses which will carry a new drive, about to be born. In the evolutionary present, the directional activity of all unicellular consciousness has been multiplied and amplified, focussed and brightened, into the flame of abstract thought. Thus, through this long distance development of our nervous system there has arisen that Hierarchy of powers which we call the brain and in Frederick Tilney's phrase "the Master organ of life." But there is also a similar phylogenetic development of behavior and personality. Each individual, as he grows from the embryo to the adult, is a little cycle of the race. We have long known that from the egg to death, we pass through stages in our body at least similar to those through which humanity has passed before. Freud has now made it clear that in our emotions, in our urgings, in the preponderance of this instinct over that at different periods of our lives, we have a like evolution and,—if we live into senility—devolution,—of personality. He has shown the child as indeed no angel, but rather, at the age of five, a polytheistic savage, having for his authority, and, too, his private pleasure, a genius loci in every tree and star, and at ten, a kind of Nazi, naturally characterized by restricted imagination, hypertrophied tribal emotions, and truculence towards other tribes; he is regimented in ritual, totally intolerant, and,—to offset his annoying sense of inadequacy,—brutally contemptuous towards all those he thinks weaker than himself. Freud has insisted that the child's sexual instincts emerge by gradual progression from an emotional pre-

occupation with one orifice of its body to an emotional preoccupation with another. However, Freud himself doubts the therapeutic value of this contribution of our knowledge of ourselves. But at least his teaching makes clear how our instincts have developed within the microcosm of each man's body and,—if inherited endowment be lacking by which to attain maturity,—how a man, or masses of men, may "stick" at the different instinctual levels. However, as regards some of Freud's other conclusions, I feel that while, bodily, we have still vestigial remnants of our past, like gill-slits, and, emotionally, others, like sexual reversions, it is absurd to attempt to estimate the total adult body in terms of gill-slits, or the total adult personality in terms of an uncovered sexual reversion.

However, when we lose what we last acquired we uncover the pattern we had acquired before. The proverb says of the Russian, if you scratch him, you will find a Tartar. It is no more true of the Russian than the rest of us. If you scratch the surface you will find, below, the more ancient, the more primitive man.

And where do these patterns come from? They come from the reception of outside and inside impressions, over ages of time, into the brain and body where they are focussed and worked up into ideas and re-creating notions. There have been those who believed the world to be a subjective experience of our own senses, who denied the very existence of anything of which man is unaware. Descartes and Locke and Kant thought of a homocentric universe, in the days before the progress of knowledge forced us to the realistic renunciation of our own ultimate authority. We no longer can believe that the existence of a thing depends on our perception of it; and contemporary thought is amazed that so flattering a philosophy was ever acceptable. Centuries of thinking had to be done before the obvious implications of the discoveries of Copernicus were applied to our own relationship with that world lying apparently about us and outside ourselves. These idealists agreed with Alice in Wonderland that I would go out like a candle as soon as you all stop thinking about me or regarding me or perceiving me. But my withers are unwrung by any such terroristic threat; common sense tells me that when you all drop into coma, I shall continue to exist, as unconcerned and as untrammelled in function, as I should be at the bedside of a patient suddenly stopped in his talk with me by an epileptic convulsion. I warn you I am as immune from summary dissipation of my atoms and their constituent particles of energy as if I had suddenly ceased being viewed and considered by a man just run over by a truck!

Nature, except to our especial senses, is impalpable and without what we call substance (a great mathematician has shown the grin to be as real as the cat). And that word "impalpable" offers a clue to the dualistic difficulties which have beset our thoughts and lamed our progress for two thousand years. Indeed, as I have already petulantly complained, we have only a dualistic vocabulary with which to combat dualism. "Impalpable" means unseizable by our senses. But these, our senses, after all, have, through millions of years of development, been produced in the fulness of evolutionary effort so that we might be able to make

contact with the universe and nature around us in at least one aspect, though that only in their sensual terms. But remember, had we a different set of senses the world, as we know it, would be changed utterly to some other fabric of some other dream. Our senses give us the working world of common sense. We can adjust and direct our activities within their framework as well as may be, allowing for their inaccuracies the while.

Once in the Sahara, I saw, it seemed miles away, a great lake with a few palm trees and some tallish isolated buildings. I kept my attention on this appearance, which endured for half an hour as I advanced toward it. About two miles from where I had first seen the mirage, I found the same number of low cacti as I had counted palm trees, and the same number of low Bedouin tents as I had counted houses. As Hume has told us, pure sense perception cannot provide data for its own interpretation.

Indeed there is a vast universe we cannot touch, that we can only imagine, and indeed we cannot imagine it. We can only surmise in abstract thought, by speculative projection through the poetry of mathematics and emotional aspiration, that it exists at all. It is impossible for us really to envisage the universe from even a dog's-eye point of view.

Religion has always served us in this purpose: the earliest Art-Form, giving a frame to the unknowable so that we may know and use it a little. At first, man made religion as a shield against his ignorance of the appalling happenings by which he found himself surrounded. And now, that the notion of geological Time and light-years of Space has given way to one of a Cosmos knowing neither, constantly turning itself inside out, at the same time expanding to infinity, (and it can't be for nothing that the ancient symbol of eternal-infinity was a serpent swallowing its own tail!) we find our emotional natures such little things that we need as much as ever the Arch-Pattern of Religion as a shield against our knowledge of the greatness of our surroundings and the smallness of ourselves.

Lately I was being helped to dress by a German man-servant. Like old soldiers, of course we talked about the war. When about to hold my dinner jacket for me, he told me that when the Revolution came he had been billeted in a house where, two days earlier, the fourth son had died. As he went behind me with the coat he said, "it makes you think there is no God." I put my right arm half into the sleeve as he held the coat. To do so, I turned my head, and our eyes met. With fierce intensity, he said "Doctor! do you think there is a God?" He had me pinioned and in a defenseless position; the fierceness too of his interrogation demanded reply. Without hesitation I said "yes, Fred, I am quite sure there is a God, but I am less sure that there is such a thing as a man." This answer allowed me to get on my coat, and he said then in a wondering tone "that is a strange saying, what do you mean?" So I had to think it out, and answered "each of my blood cells lives about thirty-two days, they are born as embryos and infants in the marrow in my long bones. Through adolescence, they grow to maturity; they are highly complex in structure, and they have a baffling variety of duties. Seen with a telescope from Mars they would appear as purposeful in their activities as do men. They fight; they are officered and

battalioned for various actions; where their country is invaded they give battle, and many lay down their lives; many more are wounded in the wars—and limp, wounded, inefficient,—perhaps on relief,—throughout the remainder of their lives. But, ill or maimed, they are gathered to Abraham's bosom in my spleen, —and I don't know the name of one of them; nor, indeed, would I even guess at their existence, if Loewenhoek had not invented the microscope and had somebody not told me how to use it. Who knows but that we humans may be the blood corpuscles of the world or of God Himself?"

The unconscionable number of cells of the brain and body are perhaps as individual as any one of us, doing their work as efficiently as any of us, gathering their energies and sending them out in orderly fashion, reproducing themselves in their own image, as capable of explosion as any of us, as capable of disorderly conduct as you or me.

It has been the fashion for the last twenty-five years to discuss mental illness as though the mind were like Mahomet's coffin, swung, unsupported, in the empyrean between heaven and earth, without pathology or structure. I am convinced this is an error. The abnormal psychology that we have been familiar with in the last twenty-five years is in the nature of a description of mere phenomena and productions or of rather pontifical postulates on their environmental dynamics. It more than tends to ignore physiological genesis and implications. We talk of the modern brand as an analysis. It is so far from really plumbing the depths of mental origins that it is but fancy figure-skating on the surface of the problem. The real problem is why does a certain person have to substitute something else for his difficulty in order to relieve his difficulty? And why does another person not have to go through that complicated procedure in order to be happy? The true problem is the nature of the play through ill or well patterned structure of positive or negative forces in the individual causing the stable or unstable equilibrium of his feelings and his intellect. The difference between one individual and another is here in modern psychology only described and not explained. But life itself depends on conflict, on forces mutually opposed; each force has its ebb and flow so that vital organisms fluctuate in character forever. They are never exactly the same in any two periods of time. They trap energy and transmit it. According to their variety of fabrication, the expression of power of which they are capable changes,—great or small, good or bad, self-preserving in the sound organism, self-damaging in the organism less sound. Indeed the very title of this address, is, to me, absurd. For there can be no such thing as correlation of mind and body; the two are the same thing. Aim is the characteristic of every vital cell; consciousness is merely the focus of the aggregate aim. Mind, to think of it in imagery, is to the Body as the flower is to the tap-root, different but the same, the same but different; it may well be that the flowering bulb corresponds to the flowering of self-awareness from the primitive homogeneous consciousness of the earlier organism. So we must not mistake the projections and the productions of the mind for the deeper causes of those projections and productions. And the cause of the projections in the last analysis lies in the type and quality of brain, body, and experience. These

center our impulses and control the weather in our souls. But the whole body, blood, bone, and muscle, our internal glands,—our sympathetic nervous system, play their complex parts, and the result is function of mind. The body is a nexus of consciousness, of which the brain is the essential switchboard, and mind is to the body as the function of Sight is to the eye. But should we think of Sight with no regard to the eye nor the brain, where it will be gathered, sorted, accepted, or rejected, and with no regard for the psychology of Vision, we should know nothing of sight. Lacking such consideration we would be regarding not Sight but aesthetics, visual aesthetics, and we should be dwelling in this, too, as among the Mysteries.

From this it follows that the function of mind can only work in the dimensions of the frame of our inheritance. We forget to apply to the human being, truths which are perfect platitudes applied to polo ponies. Christ did not. Christ knew better and said, "Do men gather grapes of thorns, or figs of thistles?" He loved the weak and the forgotten man but, in this scornful question, He is an Aristocrat of the intellect speaking the known facts of biological knowledge.

People differ in their inherited endowments, Thomas Jefferson and Dr. Watson notwithstanding! Nor am I at all sure that "inherited endowment" should be an absolute fixed concept. I challenge the dogma that there is no such thing as the inheritance of acquired characteristics. Indeed, part of our trouble in this whole discussion is that we see the problem narrow and we see it short. We think in far too small units of time. The visible, observable functioning of our body, its growth and senescence, and our sense of "the dread Fury with the abhorred shears, that slits the thin-spun life" sets for us an absolute time-scale from which we seldom emotionally recover. We cannot see the results of inheritance of acquired characteristics because of the paltry shortness of our own lives and, because our eyes are holden, our minds are holden also.

There is much evidence in the animal world that such transmission of acquired characteristics exists, that a defective germinal cell will produce a defective descendant and that the defective descendant will procreate a defect in his descendant. If this can happen in the lower animals it may happen to us; only our nervous systems are so complex, they are so much more evolved, that we cannot see changes in them in the span of our little lifetimes. And ages of effort may and do produce an improvement in the general pattern of brain and body. It is certain that if we do not stimulate the central nervous system from environment, it does not properly develop. The idiot rendered so by deprivation of special senses has special corresponding sense areas in the brain undeveloped, not because these special centers in the brain were not born properly but because they were never properly impinged upon from the outside world. For instance, in Laura Bridges, born deaf and blind, it was found after death that the areas of vision and the areas of hearing in the brain had not developed. But the initial error lay not there; it lay in the ears and eyes, in the outlying, supplying apparatus; a lack here of Nurture rather than Nature.

So the pressure of sex, the pressure of hunger, the pressure of the herd, impinge on and mould, modify and direct the organism and its personality expression.

Focal disorders may come from emotional opposition, as gastric ulcer from unhappiness and strain; and in both civil and military life, we've all seen fright produce hyperadrenalism and acute enlargement of the thyroid. Many allergic persons react to their specific protein only when their autonomic systems are, as it were, "triggered" by emotion. However, this shadow-country where the saints dwell is perhaps the Never-Never Land of Medicine. If we should learn it enough for geography and charts, we might learn to control personality and so lose our humanity. However, the stupidity of statesmen and apes in aeroplanes may be relied on to destroy civilization before disaster can reach us by our knowing what should not be known!

No army hopes to succeed without an Intelligence Corps and a General Staff to gather and sift facts and near-facts from fiction, and to bring a resultant of forces from the whole. For this in our work we need a Science of Man,—A Science which may be found to have rules of its own, hypotheses of its own, and relationships of its own. For it will have to deal not only with man as an entity, variable in his own terms, but variable too in terms of his environment, social, material and cosmic. We must use technique to gather information; we need intuition, and a sense of history and Philosophy to integrate it.

Almost in our own times have we become aware of our own evolution, and we have been here perhaps many hundred million years— a tenth of the time that life has been upon this planet. Mankind is just departing from his nursery; he stands, bright-eyed with new knowledge of his forebears and, for the first time, with the power and zest to mould his destiny. It must have been a murderous need that made, so many ages ago, a superior water-creature take to the Land, but it was a fiery thought that made man take to the Air. And how far he may yet project his power and personality we cannot even guess. The most complex things are the infinitely little and the infinitely vast,—the ultimate nature of the atom and the ultimate nature of God. Between these two mysteries is the range of our knowledge and, maybe, the wheel coming full circle, the secret of the one will be found as the secret of the other.

We are still so larval in our growing that to try to storm the seat of Zeus is to court failure and the fate of the Titans. Nevertheless, we must needs grapple ardently with the problem of Reality, whilst leading our lowly lives and earthly fates. The Stretch and Thrust, upward and outward, of aspiring thought forces brain growth and makes for almost conscious evolutionary development.

Of course we have as yet a likeness, when we would assault Heaven clamorously for Knowledge, to a winged and irridescent beetle in my cellar trying with all his little might to make up his mind whether or not I am going to Copenhagen next Summer when I cannot know myself. The beetle must fail in his impossible aim, but the ardour of his passionate thought, and the mystical ecstacy, vouchsafed to a few of the more finely organized beetles, will,—aided, of course, by their most happy faculty of rapid generation,—pile ability upon ability within them. So, one day, the nature of the deity in the drawing-room upstairs may become dimly apprehended by some poetic beetle, given to mysticism, and of a very superior order.

For the Vision is only to him who will see it.

SOME OBSERVATIONS CONCERNING THE RELATIONSHIP BETWEEN MULTIPLE SCLEROSIS AND CHRONIC EPIDEMIC ENCEPHALITIS

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When one compares neurological text books published at the end of the last century with those of today, it is remarkable how many diseases seem to have changed their character. The same holds true for the clinical material encountered in the hospitals.

In cerebrospinal syphilis, gumma has almost completely disappeared. Tabes dorsalis, which used to be a painful and progressive disease, is now relatively mild and benign.

The picture of multiple sclerosis is now dominated by a spastic paresis of the lower limbs, terminally combined with a transitory retrobulbar optic neuritis, resulting in a temporal optic atrophy. The classic Charcot's picture with nystagmus, intentional tremor and scanning speech is now rare.

To some extent this might be due to the fact that the descriptions of the clinical features of multiple sclerosis in the past century originated mainly in infirmaries for chronic diseases. Nowadays the initial stages of the disease admitted to a neurological clinic are readily recognized.

The possibility that multiple sclerosis, like syphilis, has modified its character during the passing years, must also be considered. Such a changing of the types of disease has been observed to a marked degree in chronic epidemic encephalitis.

Some years ago I reviewed the material in the neurological department of Kommunehospitalet in Copenhagen (published in a paper in honor of Haskoveo, 1936). I then had the impression that the acute cases with somnolence and diplopia had become rare although they had not disappeared. Myoclonia, a common symptom in 1920 and thereabout is seen very seldom nowadays. The Parkinsonian forms are steadily increasing. During some years the benign lymphocytic meningitis (probably of epidemic-encephalitis-origin), were very common. They are now rare. Mixed forms are still observed in rather large numbers. If radiculitis is to be regarded as a form of chronic epidemic encephalitis, a problem to be discussed later on, it must be considered a rather common occurrence during the past years.

A form of chronic encephalitis, probably belonging to the epidemic group, is the type resembling multiple sclerosis in its later stages.

The following is an illustrative example.

A young man becomes febrile, he is at the same time somewhat dull and tired and complains of diplopia. The fever and dulness diminish, but there develops a slight hemiparesis. It improves, but subsequently he develops a spastic paraparesis of the lower extremities and later a central scotoma appears in the right visual field. He has difficulties with the micturition. Somewhat later

anesthesia of the left arm developes. The abdominal reflexes disappear, and there is a bilateral Babinski sign.

Syphilitic disease is eliminated as the serology is negative. The disease fluctuates. For a period he seems almost cured, then an eye-muscle palsy appears but partly recedes again.

If you present such a case to several neurologists, one of them will say it is a typical case of acute multiple sclerosis. Another one might call it disseminated encephalomyelitis. A third will emphasize the initial stage and say it is an epidemic encephalitis, resembling multiple sclerosis. A fourth one will raise the question of the possibility of an abortive atypical case of "neuromyelitis optica."

Confronted with these diverse opinions one is inclined to ask if there is not something wrong in the neurologic terminology and the neurologic classification.

Returning to the illustrative case two problems must first be considered: the possible etiology of the disseminated sclerosis and the definition and demarcation of the epidemic encephalitis.

In order to obtain a demarcation of the disseminated sclerosis we resort to our anatomo-pathologic experiences. In multiple sclerosis the terminal stages present a destruction of the nervous tissue in the brain and spinal cord in strictly delimited foci, in which the destroyed nervous tissue is substituted by fibrillar neuroglia. The initial stage is a dissolution of the myelitic substance (later on also of the axis-cylinders) and a corresponding slight inflammatory process in which predominatingly scavenger-cells remove the destroyed myelin.

We do not know the reason for this demyelination. According to all our experience it is not very likely that it is due to bacteria, but this fact does not exclude the possibility of its being caused by an invisible virus. The question is then: Might the demyelination be due to an intoxication or a deficiency-disease, an avitaminosis, or is it more likely caused by a virus?

In my opinion a certain fact seems contrary to the theory of it being an avitaminosis or an intoxication. That is the irregular distribution of the plaques.

We are going to consider some nerve diseases, which doubtlessly are deficiency diseases: beri-beri and myelopathy related to pernicious anemia. One of the most characteristic features of these diseases is the strict symmetry of the processes. A spinal cord afflicted by anemic myelopathy presents a striking symmetry of the destruction within the posterior columns and the pyramidal tracts.

If we further consider typical toxic polyneurites, like the arsenical polyneuritis or the alcohol polyneuritis (whether we consider it as purely toxic, or combined toxic-avitaminotic), it is again marked by symmetry.

Consider, on the other hand, two infectious diseases, one caused by spirochetes, the other by an invisible virus, syphilis and poliomyelitis; they are characterized in most cases by the irregular distribution of the processes in the central nervous system. A disease like acute anterior poliomyelitis, produced by a very small virus, presents a marked irregular, asymmetrical distribution of the anatomo-pathologic findings, and the consequent paralyses and atrophies.

This is not strange. A toxin like arsenic acid or alcohol is more likely to be

distributed evenly, while bacteria and virus are much more likely to be caught somewhere in the irregular ramifications of the blood stream.

The above meditations are, of course, no proof. But lacking any proof whatsoever as to the etiology of multiple sclerosis I consider it justifiable to regard the marked irregularity of the distribution of plaques as a strong argument in support of the hypothesis that multiple sclerosis is caused by an invisible virus.

The next problem is how to mark the limits of epidemic encephalitis.

There is something fascinating in a historical characteristic of a disease, especially if it is attached to a name like that of Sydenham, V. Basedow or Charcot. But this means at the same time a great danger. The life and the mutations of bacteria and of virus are not governed by the laws of the human history. Neurological text books and hand books like to mold the diseases into certain fixed forms, often characterized by the name of an investigator. This may be justified for some diseases, e.g., Huntington's chorea, a disease which is very monotonous and invariable in appearance. The danger, however, is great in bacterial and virus diseases in which the noxis may vary.

The first description by v. Ecónomo of lethargic encephalitis in 1916 is still a classic contribution. The causative virus, however, has been modified during the years, possibly also the reaction of human beings to the virus. Therefore, there does not exist any biologic justification for molding the encephalitis-term into fixed forms, which the disease happened to show at the time when v. Ecónomo gave his classic description.

The process which must be used, in my opinion, in distributing the infections of the central nervous system, is the following: In a series of diseases, the bacterial etiology is fixed. This applies to syphilis and many forms of meningitis (meningococcal, pneumococcal, etc.). In other nerve diseases like acute anterior poliomyelitis, or lyssa, the picture of the disease is, in most cases, so well established that we, at least at present, may suppose that every one of them is caused by a relatively invariable virus.

The above large group leaves a certain number of central nervous system diseases which are (including diseases of meninges and roots) characterized by an intermittent chronic course. Some of these diseases are: lethargic encephalitis, chronic epidemic encephalitis, benign lymphocytic meningitis, radiculitis, multiple sclerosis, disseminated encephalomyelitis. Other more acute nervous diseases such as St. Louis encephalitis, encephalitis japonica, etc. must also be considered in this connection.

There are many features common to all these diseases: They are chronic intermittent diseases of the nervous system. They are probably not caused by bacteria. They are probably not toxic or avitaminotic. They are probably all caused by an invisible virus.

The next question is whether all these diseases are produced by the same virus. It is quite possible. A cavernous phthisis and a miliary tuberculosis are two variations of the same disease, although the anatomo-pathologic pictures are very different, as are the clinical pictures.

The difference in the clinical and anatomo-pathologic picture in multiple

sclerosis and in epidemic encephalitis does not prove them to be conditioned by two different viruses.

Moreover, it seems probable that the neurotrope viruses are not fixed in invariable species. It seems likely that they vary from year to year. It is possible (but not absolutely proved) that the virus of multiple sclerosis represents a variation of the virus of epidemic encephalitis. The many transitorial forms between the two diseases may support this possibility, but they do not prove it. Cases may be found in which it would have been impossible, before the time of Wassermann, to make the differential diagnosis between cerebral syphilis and multiple sclerosis. Such instances do not prove that there exists transient forms between these two diseases, only that our diagnostic abilities are imperfect.

It is to be hoped that the future will give us serologic reactions or microscopic observations, which will allow us to distinguish between the different forms of neurotropic invisible viruses.

But until we have gained such knowledge it is impossible to make an exact, scientific, distinction between these different forms of inflammations in the nervous system. Clinical descriptions of outspoken types such as lethargic, Parkinsonian, radiculitic, multiple sclerotic, etc., are possible but we have still no way of establishing whether they are clinical variations of the same disease, or whether they are etiologically different diseases.

SOME ASPECTS OF "LIBMAN-SACKS DISEASE"

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INTRODUCTION

For some time it has been evident that there is need of a clarifying publication on this disease. One source of confusion has been the rather widespread idea that the concept of the so-called "Libman-Sacks disease" includes the necessary presence of a macroscopic endocarditis of the type described by Sacks and myself. This difficulty has been due largely to the title of our 1924 paper—"Atypical Verrucous Endocarditis". However, if the later literature had been followed closely the confusion could have been dispelled.

In our 1924 paper we described four cases having about the same general clinical picture. In all there was present the peculiar form of endocarditis and in only two, lupus erythematosus. It is well known, of course, that lupus erythematosus frequently occurs without any macroscopic endocarditis, even of the thrombotic variety. It was evident that there existed a disease in which the lupus could be absent or the endocarditis could be absent. Somewhat later it was considered possible that cases would be encountered in which both the lupus and the atypical verrucous endocarditis were absent. This proved to be correct, as the subsequent notes clearly demonstrate.

There were occasional references to the fact that the clinical picture described by Sacks and myself could occur without the atypical verrucous endocarditis but it was not until 1938 that I emphasized this view in print (9). Had attention been paid to this publication the current difficulty would have been averted. In it I pointed out that even when such an endocarditis is present it is not really responsible for the clinical picture. "The endocarditis, when extensive, may well add to the general picture, but is not of itself responsible for it." As regards the so-called vascular concept, I said, "The arterial changes found in the disease cannot be considered to be in themselves responsible for the clinical picture of the disease, because they may be entirely absent. Of course, when present, especially in the kidney, they add significantly to the clinical picture, as they may, at times, in rheumatic fever."

The contribution of Louis Gross, in discovering the peculiar histologic changes of atypical verrucous endocarditis in the endocardium and pericardium of the majority of cases of lupus erythematosus unaccompanied by a macroscopic endocarditis, did much to clarify the whole subject.

As it surely will be some time before I can prepare a necessarily extensive paper on this subject, I have decided to make this short publication now. I believe that it will suffice to make a number of points clear.

I. NOTES ON SOME PAPERS RELATED TO THE DEVELOPMENT OF THE PRESENT NOSOLOGIC CONCEPT

1. Kaposi (Moriz Kohn): Neue Beiträge zur Kenntniss des Lupus erythematosus (1872).

Description of a cutaneous lesion with constitutional symptoms that may be

severe and often lead to a fatal termination. In this paper, among other data, there are notes on the occurrence of arthritis, pleuropulmonary complications and lymphadenopathy. The lymphadenopathy is considered related to the eruption (cf. 8).

2. Libman, Emanuel and Sacks, Benjamin: A Hitherto Undescribed Form of Valvular and Mural Endocarditis (1924).

Description of four cases, all showing the same distinctive clinical picture, two with and two without skin manifestations, and all showing a form of endocarditis (atypical verrucous endocarditis) which had not been previously described. This showed that the clinical picture first described by Kaposi (and amplified by later observers) may occur in the absence of any eruption.

3. Gross, Louis: The Heart In Atypical Verrucous Endocarditis (Libman-Sacks) (1932).

A more detailed study of atypical verrucous endocarditis. Description of certain histological changes which in a later paper by Gross were claimed to be diagnostically characteristic.

4. Tremaine, Myron J.: (Pupil of Christian). Polyarthritic Symptoms; Polyserositis; Glomerulonephritis; Progressive Secondary Anemia; Sterile Blood Cultures; No Endocarditis or Aschoff Bodies in Myocardium. (1934).

Description of two cases. Realized that a disease occurred with a peculiar clinical picture which could be accompanied by lupus erythematosus or not, and pointed out the difficulty of putting the cases into any known nosologic group. Suggested that the disease might be considered a form of Pick's disease.

5. Christian, Henry A.: Long Continued Fever With Inflammatory Changes in Serous and Synovial Membranes, and Eventual Glomerulonephritis: A Clinical Syndrome of Unknown Etiology (1935).

Recognized early that there existed a peculiar disease which could or could not be accompanied by a cutaneous lesion. Regarded the condition as a disease which requires proper designation. "The condition constitutes a definite clinical syndrome recognizable as such during the course of the disease. At present no satisfactory name for the syndrome occurs to me other than the quite cumbersome descriptive heading that forms the subject of this brief description. It is some type of infectious disease of unknown etiology."

6. Baehr, George, Klemperer, Paul, and Schifrin, Arthur: A Diffuse Disease of the Peripheral Circulation (Usually Associated With Lupus Erythematosus) (1935).

Description was given of vascular lesions of the disease and it was claimed that the disease was one of vascular origin ("vascular concept"). As is well known, a similar view was held by H. Keil (17a, 17b). It did not appear to be correct because it was known that the disease could occur in the absence of vascular

lesions or in the presence of a few changes that might be encountered in a variety of diseases (cf. 15).

7. Belote, G.H., and Ratner, H. S. V.: So-Called Libman-Sacks Syndrome: Its Relation to Dermatology (1936).

Called condition "Libman-Sacks syndrome." Believed that it should be classified under the Osler syndrome. This was not a correct conception because Osler stated that he believed that cases corresponding to the syndrome might be due to a variety of causes. It is now believed probable that at least two cases in Osler's series (19 and 26) belong in the category of Libman-Sacks disease.

8. Friedberg, Charles K., Gross, Louis, and Wallach, Kaufman: Nonbacterial Thrombotic Endocarditis Associated With Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions (1936).

These cases, which were associated with nonbacterial thrombotic endocarditis (this lesion not being specific nor significant), were characterized by prolonged fever, deforming arthritis, involvement of serous membranes and widespread vascular lesions. Lymphadenopathy was conspicuous in one case. The authors suspected that these cases represented a form of what is now called Libman-Sacks disease. On later study of three cases from which sufficient pathologic material was still available, the histologic lesions, which were described by Gross as characteristic of Libman-Sacks disease, were found in the endocardium and pericardium in the absence of any macroscopic atypical verrucous endocarditis. This publication is valuable because it led to more attention being paid to the form of Libman-Sacks disease characterized by deforming arthritis and conspicuous adenopathy (see 16, György), without any evidence of lupus erythematosus.

9. Libman, Emanuel: The Varieties of Endocarditis and Their Clinical Significance (1938).

"In other words, we have here a generalized disease in which there may be present the endocardial vegetations alone, the lupus erythematosus alone, both conditions, or neither."

10. Reifenstein, E. C., Reifenstein, E. C. Jr., and Reifenstein, George H.: A Variable Symptom Complex of Undetermined Etiology With Fatal Termination Including Conditions Described as Visceral Erythema (Osler), Disseminated Lupus Erythematosus, Atypical Verrucous Endocarditis (Libman-Sacks), Fever of Unknown Origin (Christian) and Diffuse Peripheral Vascular Disease (Baehr and Others) (1939).

Recognized that there existed a disease that could occur with or without cutaneous lesions, which had been described under a number of designations.

11. Ginzler, Arthur M., and Fox, T. T.: Disseminated Lupus Erythematosus: A Cutaneous Manifestation of a Systemic Disease (Libman-Sacks). Report of a Case (1940).

Considered lupus erythematosus to be one manifestation of a systemic disease.

12. Gross, Louis: The Cardiac Lesions in Libman-Sacks Disease With a Consideration of Its Relationship to Acute Diffuse Lupus Erythematosus (1940).
Detailed description of the histologic lesions of atypical verrucous endocarditis as found in the endocardium and pericardium in cases of the disease with or without disseminated lupus, and with or without macroscopic endocarditis. Because the same histologic lesions were found in cases having the same clinical picture, with and without lupus, and because of other considerations, author advised calling all the cases Libman-Sacks disease, leaving lupus erythematosus as the name of the characteristic eruption. This suggestion is being rather widely followed.

13. Proger, Samuel: Acute Disseminated Lupus Erythematosus, or Libman-Sacks Disease, or Subacute Non-Rheumatic Arthro-Serositis (1941).
Conceives disseminated lupus erythematosus as part of a general condition for which the designation "subacute non-rheumatic arthro-serositis" is suggested.

14. Banks, Benjamin M.: Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? (1941).
The implication is sound. The common denominator is a systemic disease in which scleroderma, dermatomyositis or lupus erythematosus may or may not be present, and if present, appear in various combinations. Necrotizing arteritis (so-called periarteritis nodosa) may occur in this disease as in a number of others.

15. Klemperer, Paul, Pollack, Abou D., and Baehr, George: Pathology of Disseminated Lupus Erythematosus (1941).
Authors say, "The characteristic organic changes, previously considered as heterogenous, can now be understood as local manifestations of the widespread damage of collagen." They add that, "Various concepts of lupus erythematosus as a disease with predominant localization in a single organ or as a diffuse disease of the peripheral circulation can be entertained no longer." In other words, the so-called "vascular concept" is withdrawn. Although the authors state definitely that the disease should not be considered as having a predominant localization in a single organ, they call it lupus erythematosus and do not propose any other designation for cases of the disease in which there is no cutaneous manifestation.

16. György, Paul: Still's Disease, Chronic Rheumatoid Arthritis and So-Called Disseminated Lupus Erythematosus (1942).
Consider lupus erythematosus a cutaneous manifestation of a systemic disease and suggests that Still's disease and chronic rheumatoid arthritis in children be included in this category.

In October, 1941, I discussed the nosologic relations of Libman-Sacks disease at the Sinai Hospital in Baltimore. Among the conditions that were taken into consideration were infectious arthritis, arthritis deformans and Still's disease.

I stated that I suspected that at least some cases of Still's disease belong in the category of Libman-Sacks disease but that I did not have any definite proof. To make sure, one would have to find, at necropsy, in such cases the lesions of atypical verrucous endocarditis, macroscopic or microscopic. Other useful evidence would be the presence of the "hematoxylin-staining bodies" of Gross, the signet-cell lesions in the pericardium, the wire-loop glomerular lesions and perhaps the characteristic periarterial fibrosis in the spleen.[1]

Dr. György's idea was completely independent. I had nowhere put my suspicion on paper.

GENERAL CONSIDERATION

These brief notes show an interesting nosologic development. First Kaposi described what was considered to be a cutaneous disease (lupus erythematosus) with visceral involvement. Then it was learned that in this disease there occurs a peculiar form of endocarditis. This and other observations led to the knowledge that lupus erythematosus is the cutaneous manifestation of a general disease which also occurs without it. It was also learned that the disease can occur in the form of the Osler syndrome, arthritis deformans or infectious arthritis (possibly Still's disease). Further, it developed that some cases of scleroderma, myositis and dermatomyositis belong in this category and that the disease may appear first as a simple glomerulonephritis or as purpura hemorrhagica. Necrotizing arteritis may occur, as it may in a variety of diseases. The lymph node involvement in the disease may be so striking as to mislead the observer into believing that he is dealing with a form of the well known primary diseases of the lymph nodes. The relationship of discoid lupus to the disseminate form has not been definitely determined but there is a tendency to believe that it is possible for the discoid form to disseminate (18, 19). The case reported by Edelman (22) is of particular interest in this connection. In

[1] This was observed first by Sacks (noted in paper by Libman and Sacks). It was later described by Klemperer in a case published by Denzer and Blumenthal (20). Ginzler and Fox (11) noted the lesion in their case (see Fig. 10, page 37 of his paper). In the paper by Klemperer, Pollack and Baehr (15), the lesion is noted as being present in 19 of the 20 cases studied by them. It is described by them as "a peculiar periarterial fibrosis limited to the central and penicillary arteries." They considered the lesions specific. Kaiser (21) studied the incidence of this periarterial fibrosity of the spleen in 1,679 control cases. In a series of "consecutive routine autopsies" the lesion was found in 22 of 970 cases or 2.3 per cent. In a second "series of cases selected for special clinical or pathological features," 709 in number, the lesion was found 31 times or 4.4 per cent. In the total study of 1679 cases the lesion was found 53 times or 3.2 per cent. This is a small percentage. It is very likely that the percentage would be still smaller if all these cases were studied from the standpoint of the possibility of their being examples of Libman-Sacks disease. Evidently no consideration was paid to cases of the disease in which the skin eruption was absent. Among the categories in which the lesion was found are noted "rheumatic fever," "acute splenic tumor," "chronic passive congestion of the spleen," "anemia," "periarteritis nodosa," and "essential thrombocytopenic purpura." The highest percentage was found in the cases of purpura. It would be of particular interest to study carefully the records of these cases of purpura in order to learn whether any of them can be interpreted as being examples of Libman-Sacks disease.

his patient, who was suffering from discoid lupus, visceral dissemination took place with a fatal issue (purpura, renal lesions) without dissemination of the lupus.

II. SIGNIFICANT FEATURES OF THE DISEASE

1. *Etiology:* Unknown.

2. *Sex:* Predominance in females.

3. *Duration:* Months or years, with or without free periods. Febrile disease characterized by waves in which one or more organs may be involved. Other organs may be specially involved in a recurrence, in various combinations.

4. *Fever:* Variable type, usually irregular. Constant symptom.

5. *Joints:* Arthralgia; acute swelling or more subacute effusion; deformity; ankylosis. Arthralgia and arthritis most common local manifestations—occur in practically all cases, usually early.

6. *Cutaneous lesions:* Lupus erythematosus—frequently; dermatomyositis; scleroderma; urticaria—very infrequently; Osler nodes—rare. Petechiae (also white-centered) and purpura. Lupus, if present, may come early and disappear rather quickly or persist, or it may occur only in a second or third wave of disease, or only shortly before death.

7. *Lymph nodes:* Discrete, moderately or greatly enlarged, or in large packets. These large packets have been noted in the cervical region, the axilla, the mesentery, the retroperitoneum, and, in one case, along both sides of the trachea. The histologic picture varies. It may present an appearance like that of an ordinary hyperplasia or resemble giant follicular lymphoblastoma or Hodgkin's disease, and there may be present the "hematoxylin staining bodies" of Gross, or macroscopic necroses.

8. *Kidneys:* Diffuse vascular-glomerular disease; occasionally glomerulonephritis. Hypertension usually not present.

9. *Lungs:* Pneumonitis very frequent—often appears early. It may resemble lobar pneumonia, or a localized bronchopneumonia; there may be numerous scattered foci throughout both lungs. Occasionally large perivascular inflammatory areas. Purulent lesions and empyema occur only with terminal secondary infections by streptococci or staphylococci. (This subject requires much further investigation.)

10. *Polyserositis:* Pericarditis frequent, more often with effusion. At necropsy—pericardial adhesions frequent. Pleurisy—with or without effusion. Peritoneal involvement—occasionally.

11. *Muscles:* Myositis; dermatomyositis.

12. *Heart:*[2] Systolic murmur may be present without any involvement of the endocardium. Atypical verrucous endocarditis may be present without any murmur. All this refers to cases having no previous valvular defect.

[2] This note was made in a statement of the features of the disease prepared by Dr. Sacks for lecture purposes in 1930. A copy of it was given to me in 1936. It indicates that we learned early that even extensive endocardial lesions in the disease played no significant clinical role.

13. *Spleen:* Splenic enlargement, if present, usually moderate.

14. *Blood:* Progressive secondary anemia; leukopenia (but not always); tendency to thrombocytopenia.

15. *Brain:* Cerebral irritative phenomena, especially convulsions; peculiar stupor; palsies. (This subject requires much further investigation.)

16. *Eyes:* Papilledema; retinitis; hemorrhages and exudates. These may occur independently of any renal lesions.

17. *Blood cultures:* Negative except for terminal bacterial invasion.

GENERAL CONSIDERATION

The clinical diagnosis of the disease is very easily established when lupus erythematosus is present. In the absence of the eruption certain groupings of symptoms are suggestive of the diagnosis, or the diagnosis may have to be suspected by exclusion. An important group of symptoms is fever, joint symptoms, serositis, and renal disease. Lymphadenopathy in addition is of great significance. If leukopenia is present, fever and joint symptoms alone are suggestive. Any of the symptoms may be the earliest manifestation. The most common early symptoms are fever, joint symptoms and pulmonary involvement. In cases of scleroderma or dermatomyositis one must keep in mind the possibility of Libman-Sacks disease especially when nephritis, serositis, or lymphadenopathy is present.

The association of fibrinous pericarditis and white-centered petechiae is of diagnostic value if the blood cultures prove to be sterile. The same combination in the presence of a positive blood culture (especially nonhemolytic streptococci) points to combined active rheumatic fever and active subacute bacterial endocarditis. As is now well known, fibrinous pericarditis occurs exceptionally in subacute bacterial endocarditis, and white-centered petechiae are found practically never in cases of rheumatic fever.

The presence of the combination to which I have just referred, in cases of Libman-Sacks disease, is associated with the presence of macroscopic endocarditis. Under such conditions I refer to the case as Libman-Sacks disease with endocarditis. Similarly, when there is evidence of widespread arteritis, I speak of Libman-Sacks disease with arteritis. In general, I add the name of the predominant manifestation to the diagnosis, as for example, Libman-Sacks disease with lupus erythematosus, or Libman-Sacks disease with scleroderma, etc.

Often I am asked how one makes a differential diagnosis between Libman-Sacks disease and periarteritis nodosa. This question is really not correct. Necrotizing arteritis (I speak of periarteritis nodosa only when vascular nodules are definitely evident—this in the sense of Kussmaul and Maier) may occur in a variety of conditions including acute and subacute bacterial endocarditis, rheumatic fever and Libman-Sacks disease. In any case in which there is a suspicion of necrotizing arteritis (established clinically or as a result of biopsy) one must try to find the possible cause. As already stated, Libman-Sacks disease is one of these causes, so that in a given case of necrotizing arteritis the question that arises is whether it is part of the lesions of Libman-Sacks disease.

It is not possible for me to go fully into the extensive differential diagnostic considerations involved in a study of this disease. As an example of how peculiar the clinical picture may be, I cannot refrain from making a note of a case which was described to me by a physician who attended a demonstration at the meeting in Atlantic City, and who was particularly interested in the heading Brain—in the chart which was being shown to him. He told me that he had had under observations a patient who suffered for several months from fever, arthralgia, pleurisy and pericarditis. The condition did not appear to him to be one of rheumatic fever, especially because from time to time convulsions occurred and there were attacks of unilateral ptosis. It was not until one week before the patient died that the diagnosis was confirmed by the development of lupus erythematosus.

The great variety of clinical phenomena that may be encountered in a given case, and the variability of the predominant symptoms in different cases are due, of course, to the widespread and varying involvement of the organs (collagenous tissue, according to Klemperer and his associates). The symptoms that may occur may be due to this involvement alone, to vascular lesions, or to both.

Accordingly, we must expect in the future to find that there is even a greater variety of clinical manifestations of the disease than that with which we are already acquainted. Hartwell and Thannhauser (23), for example, have pointed out the possible relation of some cases of febrile nodular panniculitis to Libman-Sacks disease. The patient, whose history they narrate, suffered from pericarditis and pleurisy simultaneously with peculiar nodular infiltrations of the subcutaneous and fat tissue over the trunk, extremities, and face. In their comment on the case, the authors say, "(1) Nodular nonsuppurative panniculitis is not a local disease of the fat tissue. It may start with a polyserositis and simulate rheumatic fever or lupus erythematosus. (2) The cases reported in the literature as dermatomyositis comprise different groups of disease, of which a part belongs to the lupus erythematosus group. . . ." MacMahon (24) has described hemolytic icterus in one case.

The main criteria for the recognition of the disease by pathologic-anatomic study have been noted above. The histologic lesions in the endocardium and pericardium noted by Gross are: the absence of primary valvular ring involvement, and the presence of "hematoxylin staining bodies," eosinophilic multinuclear coalescent bodies, endothelial bud capillaries, and "signet cell" lesions in the pericardium. He emphasized the significance of the "hematoxylin staining bodies" and the "signet cell" lesions.

After much consideration, I have decided to adopt, for the present, the suggested name—Libman-Sacks disease. We are first in need of knowledge of the etiology of the disease, and of better methods of recognizing it during the lifetime of the patient, than those now at our disposal. Once the etiology is established, the proper nomenclature will become self-evident.

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COURSE AND PROGNOSIS IN THE PSYCHONEUROSES[1]

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One of the chief points of interest in the study of prognosis in the psychoneuroses seems to be the controversy between the exponents of various methods of treatment in regard to the relative practical values of such methods. The advocates of intensive analytic therapy claim that the chief disadvantage of the more superficial methods lies in the fact that their results are temporary and lead in many cases not only to a recurrence of the symptoms but often to the development of more serious forms of maladjustment. On the other hand, those who practice such methods as suggestion or reassurance express the view that the more time-consuming and complicated methods have not proven their superiority in the majority of cases. In some cases they feel that deep analyses may even be definitely injurious to the patient. Since this controversy naturally hinges on actual proof in the form of long-term follow-up studies of large numbers of cases, it is surprising to find that, considering the available material, the older literature is remarkably poor in systematically organized studies of the kind. In most textbooks and monographs on the subject (1) we find only general statements concerning the probable prognoses without any statistical data. Other contributions deal more with technical controversies, limiting discussion of actual results to reports of isolated cases. It is only within the last decade that attempts have been made to evaluate results statistically and several studies of this type have been reported (2). It is quite evident, however, as one reads these contributions that the main point of interest is still whether a given method of treatment is more or less likely to influence the neuroses. Some of these authors do suggest very strongly that differences in methodology seem to be much less important than has always been claimed but rather than look for significant factors in the individual patient, they attribute the variations in successful treatment to the personality and enthusiasm of the physician. For the purpose of broadening this field of investigation an attempt has been made in the present contribution to determine the importance of certain factors in the clinical picture, personality, physical status and history of each patient as these influence the course of the maladjustment, evaluating them in relationship to the method of treatment employed.

Procedure: All the cases admitted to the Iowa State Psychopathic Hospital

[1] The material upon which this study was made is from the Iowa State Psychopathic Hospital. The results were presented in part at the 96th meeting of the American Psychiatric Association, Cincinnati, 1940.

during the years 1929 to 1937 inclusive in which the diagnosis of *psychoneurosis* was made were utilized for this study. During the entire period, one of the authors (W. M.) was in charge of the clinical work of the hospital, and all the cases were examined by him personally. Their treatment by the other psychiatrists was carried out in cooperation with him and under his supervision. The records of these cases were analyzed and a number of factors considered significant were abstracted. In each case, the subsequent course was ascertained and during the year 1939 a reevaluation of the patient's present status was made. In a number of these cases this was done on the basis of actual re-examination. In others, the evaluation was made on the basis of information obtained from the patient, his relatives, acquaintances, social agencies or physician who had contact with him. It would have been more desirable, of course, to have had psychiatric examinations of all of them but it does not seem quite so important in the psychoneuroses as in other psychiatric entities. The maladjustment of the psychoneurotic patient is usually dependent upon symptoms of which he is probably more aware than anyone else, and the examiner must, in any case, depend largely upon the symptomatology as presented by the patient himself. Furthermore, the psychoneurotic patient is prone to exaggerate rather than to underestimate his difficulties. If he does not make himself conspicuous by a demonstration of his symptoms and admits to being well, the probabilities are that his disease is cured. If, in addition to that, he has gone back to his previous work and way of living, and is no longer hampered by his neurotic symptoms, we can justifiably consider him as recovered, provided this has continued over a relatively long period of time.

Material: During the designated time period, a total of 341 patients diagnosed *psychoneurosis* were admitted and treated at this hospital—155 of these patients were male and 186 were female.[2] Practically all of these were residents of the State of Iowa. (This was considered important in evaluating the results because this area is more homogeneous, racially, economically and culturally, than many other sections of the country. With these extraneous factors at a minimum, it is easier to determine the significance of variations in the personality and experience of the individual patient as they influence the development of the psychoneurosis.) All of these patients were studied and treated at the hospital for varying periods of time, the average hospital residence being about two months. The diagnoses were made at staff conferences and before the discharge of the patients. The criteria utilized in arriving at a diagnosis can be summarized in the following definition (3). "Psychoneurotic behavior reactions are manifestations of disturbances in the functions of the personality, evaluated with due consideration to social, cultural or individual settings. They may develop on the basis of certain types of personality structure but are mainly expressions of conflicting emotional trends whose nature or relationship to the symptoms are not understood by the patient. They are characterized by 1) Clinical features of a *positive* type: conversions, fugues, anankastic reactions (4) or faulty control

[2] The sex difference was most striking in the Hysterias (40 male and 80 female) and the Anxiety Neuroses (15 male and 5 female).

of emergency measures (5) and 2) *negative* features such as a lack of demonstrable, relevant organic pathology, no primary disturbance of affect, no deterioration of intelligence and no clear-cut and persistent distortions of external reality."

Each case record was analyzed as to the presence and character of these features. In addition to that a number of other data were considered. These included: 1) *Clinical:* physical build, premorbid personality, intelligence quotient and somatic pathology; 2) *Historical:* heredity, the occurrence of previous attacks; the manner of onset, duration of symptoms and the etiology; 3) *Therapeutic:* length of hospital residence, methods of treatment and the course during the stay in the hospital.

In the follow-up study, the course following discharge was ascertained, the occurrence of subsequent attacks and the manner of adjustment throughout that period preceding the present status. In order to determine the relative stability of the results of treatment, the cases were divided into two groups: 1) Those patients who were followed for five or more years. 2) Those patients who were followed for less than five years. The present status was described under the following subheadings: 1) *Recovered:* the patient is adjusting socially and economically on a level equal or superior to that preceding the onset of the disease. He has none of the symptoms with which he came to the hospital and is not considered by informants as in any way different from the average person. 2) *Greatly improved:* the patient is adjusting well socially and economically. He himself, or those about him, still notice occasional difficulties which, however, do not interfere with his adjustment or render him in need of help. 3) *Improved:* The patient still retains some of his symptoms, noticeable both to himself and to others but they do not interfere with adjustment to the extent that they did on his entrance to the hospital. 4) *Unimproved:* The patient is maladjusted to the same extent as or more than that which he showed upon admission. 5) *Unknown:* patients could not be located at the time of the follow-up. 6) *Psychosis:* patient has developed symptoms of a definite psychosis. Seventeen patients or 5 per cent of the total group died after discharge from the hospital. These were included in the particular group to which they belonged according to the clinical picture they showed before death.

Results: In table 1 the results from the whole group are classified into six sub-headings. The figures represent percentage proportions in relation to each group. The Reactive Depressions lead both in number of recoveries and in errors in diagnosis. The total number (fourteen) is so small, however, that this cannot be taken as definitely significant. The relative proportion of the different results in the other forms of psychoneuroses are in keeping with the reports of other authors. The Hysterias show a definitely more favorable prognosis, the Mixed Neuroses are next in order, followed by the Neurasthenias, Psychasthenias and Anxiety Neuroses. This last is perhaps the most striking result as it is in variance with isolated, rather optimistic reports of treatment in Anxiety Neuroses. It must be added, however, that we have not included the cases of anxiety hysteria or psychasthenic phobia in this group. Second or third admissions of patients were not considered as separate cases but were classified according to

their present condition. There were only 46 readmissions (12 per cent) in the whole group, the highest relative frequency of such relapses occurring in the Psychasthenias. An interesting point to be noted is the rather small proportion (6 per cent) of errors in diagnosis where the patient later developed a psychosis. This group of cases will be discussed in greater detail in a separate publication especially in reference to some recent reports on the subject (6).

TABLE 1

Present status of all patients

DIAGNOSIS	TOTAL NUMBER	PER CENT RECOVERED	PER CENT GREATLY IMPROVED	PER CENT IMPROVED	PER CENT UNIMPROVED	PER CENT UNKNOWN	PER CENT PSYCHOSIS
Reactive depressions	14	64	7		14		15
Hysteria	120	50	13	11	18	2	6
Mixed	109	37	20	11	23	1	8
Neurasthenia	33	30	6	15	33	12	4
Psychasthenia	45	27	29	22	18		4
Anxiety	20	20	30	15	20	10	5
Totals	341	40	18	12	21	3	6

TABLE 2

Influence of length of follow-up period upon outcome

DISEASE	PERIOD OF FOLLOW-UP	NUMBER OF CASES	PER CENT RECOVERED	PER CENT GREATLY IMPROVED	PER CENT UNIMPROVED
Mixed neuroses	Over 5 yrs.	39	46	13	18
	Under 5 yrs.	70	31	24	26
Hysteria	Over 5 yrs.	58	53	10	12
	Under 5 yrs.	62	47	16	22
Psychasthenia	Over 5 yrs.	14	29	50	0
	Under 5 yrs.	31	26	19	26
Anxiety neuroses	Over 5 yrs.	6	17	33	17
	Under 5 yrs.	14	21	29	21
Neurasthenia	Over 5 yrs.	12	16	16	33
	Under 5 yrs.	21	38	0	33

The figures in table 1 are representative of the whole group regardless of period of follow-up. Since the point has been raised by some as to the relative instability of therapeutic results in the psychoneuroses and some authors have actually reported a gradual diminution of the proportion of recovered cases as they were followed through the years, we have separated the material into two groups. The results are given in table 2. As can be seen from table 2, each of the classifications is reported in two sections: patients followed for five years or

more as they compare with those who have been followed for shorter periods of time. The results consider only the Recovered, Greatly Improved and Unimproved patients. Surprisingly enough it appears that in most of the groups the relative proportions of Recoveries vs. Unimproved cases are the opposite from what one would expect, that is, the Recoveries are relatively higher in the older cases than in the more recently discharged ones. The group of Greatly Improved cases fluctuates in the opposite direction, however. There are relatively more Greatly Improved cases in the recent discharges than in those that have been followed for five years or more. Taken together, these two groups of more or less successful therapeutic results would be about equal in the two sub-divisions. The possible interpretations of this will be taken up in the discussion. It should also be pointed out that an outstanding exception to this rule is furnished by the Neurasthenias. Here the complete recoveries are of a relatively lower proportion for the cases followed for five years or longer than they are for the more recently discharged cases. To a much lesser extent this is true also for the Anxiety Neuroses. It should be borne in mind, however, that in these two groups we are dealing with smaller numbers which do not lend themselves to adequate statistical evaluation. For this same reason, we have omitted from this table the Reactive Depression Group. In the larger groups which are statistically more dependable, the trend is sufficiently significant to justify us in dealing with the whole material rather than splitting it up into periods of follow-up as we evaluate the single factors in their relationship to Prognosis.

The evaluation of the importance of certain features in the clinical picture, method of treatment and anamnestic data as related to prognosis—that is, the establishment of criteria of prognosis—has brought out a number of factors, some of which are statistically quite significant and clinically enlightening. In table 3 only the most important of these factors are tabulated for the groups of the Hysterias and Mixed Psychoneuroses. We have chosen these two groups since they represent the largest and therefore statistically most reliable of the various subgroupings of our material. Furthermore, the comparisons were made only on the Recovered (designated "R") and the Unimproved (designated "Un") cases, partly because they represent the largest proportions within the single classification and partly because the results in terms of therapeutic success are thus more distinctly opposed to each other. The figures in this table represent percentages unless otherwise indicated. In the third row under each factor we have indicated the computed statistical significance in terms of "P" (probability) value. Thus where P = <.05> .02 it indicates that the probability of the difference being due to chance is less than 5 in 100 and more than 2 in 100.

In the Hysteria patients we find, first of all, that physical build is important.[3] The recovered cases show a significantly larger proportion of average physique and a smaller proportion of asthenics than do the Unimproved. The intelligence quotient was determined in most cases on the basis of the Stanford Revision and they were grouped into I.Q. of 90 and above as opposed to those below 90.

[3] Av.—average; As—asthenic; O—others such as athletic and pyknic.

The Unimproved cases show a definite trend toward low I.Q. A trend is also found in the duration of the maladjustment prior to admission. The Unimproved cases include a greater number of patients whose disease had begun a year or more before admission while the Recovered cases showed a preponderance in duration of a year or less. It should also be pointed out that this difference became progressively less as the basis of computation was shifted to 2, 3, 4, etc. years. The Permeability Quotient (P.Q.) showed a trend toward normal values in the Unimproved cases while the Recovered cases showed a preponderance of

TABLE 3

Analysis of single factors

Hysteria

GROUP	NUMBER	PHYSIQUE, PER CENT			I.Q., PER CENT		DURATION, PER CENT		P.Q., PER CENT		ONSET, PER CENT		THERAPY, PER CENT	
		Av.	As	O	Over 90	Below 90	1 yr. or less	1 yr. or more	Normal	Above or below	Acute	Grad.	Expl.	Others
Re	60	45	27	28	60	40	55	45	47	53	60	40	80	20
Un	20	25	50	25	33	67	30	70	69	31	44	56	65	35
p		More asthenics in unrecov- (.05).02			Lower I.Q. in unrecovered (.10).05		Longer duration in unrecov. (.10).05		More normals in unrecov. (.20).10		More grad. in unrecov. (.30).20		Less explor. in unrecov. (.30).20	

Mixed neuroses

GROUP	NUMBER	AGE		DURATION, PER CENT		HOSP. RESIDENCE		THERAPY, PER CENT		I.Q., PER CENT		P.Q., PER CENT	
		Mean	S.D.	1 yr. or less	1 yr. or more	Mean	S.D.	Expl.	Others	Over 90	Below 90	Normal	Above or Below
Re	40	32.4	9.58	53	47	1.9	2.04	74	26	56	44	41	59
Un	24	40.7	13.12	21	79	1.0	.54	48	52	40	60	61	39
p		Older in unrecovered (.01)		Longer duration in unrecov. (.02).01		Shorter resid. in unrecov. .03		Less expl. in unrecov. (.05).02		Lower I.Q. in unrecov. (.20).10		More normals in unrecov. (.20).10	

above or below normal values. One also finds in the manner of onset a trend which is interesting although statistically lower than some of the other factors. Acute onsets are more common among the recovered. An interesting point in this connection is that this difference becomes very much more accentuated ($P < .10 > .05$) when the female patients are computed separately.

The evaluation of treatment is somewhat difficult. With the psychoneurotic patients remaining in the hospital for a fairly long period of time, the general therapeutic principle at the hospital was to attempt to discover the underlying factors and most cases were treated by methods which might be designated inclusively as *deep exploration*. In some cases where lack of cooperation, inac-

cessibility, short duration of hospital stay or low intelligence made rational exploration impossible to any appreciable extent, the treatment was more or less restricted to suggestion, reassurance and one or another form of physiotherapy. It should be pointed out also, that no matter how predominant exploration may be in the therapeutic approach some suggestion is always present. In table 3, therefore, we have tabulated the treatment as exploratory (expl.), regardless of what additional methods were used, as contrasted with those cases where exploration was only superficial or was not attempted at all (others). The figures show that a larger proportion of the Recovered cases received exploratory treatment as contrasted with the Unimproved group.

The second half of table 3 shows a similar analysis of factors for the Mixed Neuroses. Although some of these follow the same trend as in Hysteria, others differ to a pronounced extent. For example, physique and manner of onset seem to have no importance in these cases. The intelligence quotient and the permeability show essentially the same tendencies as in Hysteria but the statistical significance is greater here. This is even more true with respect to the method of treatment where "P" is less than .05. We find other factors of importance, however. The length of hospital residence is definitely important since the mean for the Recovered cases is almost twice that of the Unimproved. The age on admission shows an even greater difference in that most of the Recoveries were under 40 years of age while the majority of the Unimproved were above 40. The duration of the disease before admission shows a trend similar to that in the Hysterias, but it is statistically of greater significance "P" being between .02 and .01. The other factors that were studied such as premorbid personality, etiologic factors, heredity and the various types of symptoms did not seem to bring out any criteria of differentiation that could be considered at all significant.

The relatively small number of patients in the other sub-groups rendered it impossible to draw statistically valid conclusions but some useful possibilities might be noted. In the psychasthenias it was found that the Recovered cases, as contrasted with the Unimproved, had a longer hospital residence, more acute onset and shorter duration of the disease before admission. They showed a predominance of compulsive-obsessive symptoms as contrasted with phobias and were more likely to show improvement while still in the hospital.

In the neurasthenias, the Recovered cases showed higher intelligence quotients, less of a predominance of fatigue and weakness and a higher proportion of emotional and vegetative symptoms than did those who were Unimproved.

In the anxiety neuroses the Recoveries were equally divided between males and females whereas the Unimproved were all males. Emotional and gastrointestinal symptoms were definitely more prevalent among the Recoveries than among the Unimproved. Constitutional personality factors were predominant in the Unimproved as contrasted with the Recoveries.

COMMENTS

In reporting our results we have purposely tried to limit ourselves to objective data and computations based on these and have refrained from interpretations.

There are certain relationships, however, which suggest justifiable interpretation. The general trend in the relative proportion of Recoveries vs. other results is in keeping with reports by other observers (particularly those reported by Ross and the New York Psychiatric Institute). One very important difference between our results and those reported by Ross is the "apparent" decrease in his recovered cases as the material is followed for a long period of time. The term "apparent" is used advisedly since it would seem that the main reason for this decrease may be the large number of cases which he designates as "lost sight of." There is, of course, no way in which one can tell just what the condition of these patients might be but one cannot make any definite computations on patients when (as, for instance, in his 1921 cases) 74 per cent of the material could not be located. This is rendered still more significant by the fact that as the "lost sight of" group decreases in number the recoveries go up very materially. An important point in this connection is to be considered in relation to our findings that the number of Recoveries actually increases with time and that this increase is at least partly gained at the expense of the "Greatly Improved" category. In the work with the individual cases we have frequently found that with deep exploration one may have succeeded in giving the patient an intellectual insight into his problems which may lead to further improvement after discharge from the hospital as he digests, so to speak, the newly gained understanding and has an opportunity to apply it to a real life situation outside the hospital environment.

The findings in the group of the Reactive Depression, small as their total number may be, suggests some interesting possibilities. We find here a comparatively high rate of recovery but also the highest proportion of cases which were subsequently diagnosed as psychoses. As far as can be gathered from the literature there are no generally accepted criteria for this entity and their distinction from the manic-depressive group has not been clearly demonstrated. Most of these persons are of cyclothymic personality who develop so-called "reactive depressions" under stress. It is possible that the periodicity and manic-depressive constitution may explain both the frequent recoveries and, in some, the subsequent development of manic-depressive psychoses. This question also crops up in the evaluation of the neurasthenias (where there is a possible point of contact with the constitutional psychopathies) and the psychasthenias (where relationships to the Schizophrenias have been suggested) (4).

The results of the analysis of single factors in the Hysterias and Mixed Neuroses (table 3) brings up a number of significant features. The degree of intelligence and the duration of the disease seem to be important as prognostic indices in both groups. Suggestions to this effect are found in a number of contributions and it is gratifying to find that statistically a definite tendency in this direction can be demonstrated. In a group of cases treated mainly by deep exploration it would have been surprising to find it otherwise. This is also true of the value of exploration in leading most frequently to a lasting improvement or recovery. Just what the relationship of the Permeability Quotient and prognosis may be we are not prepared to say. The figures show a preponderance of undisturbed P.Q.'s in the Unimproved cases. Does this indicate that a low or high P.Q.

may mean somatic reactions dependent upon a more active response from the organism to the emotional disturbance and therefore, a more active participation by the patient in combatting the maladjustment? At present we are not able to answer this question.

In the Hysterias, physical build and manner of onset appear to be important. This again is not surprising since, in the experience of most workers in this field, an asthenic physical build is associated with poorer resistance to the stresses and strains of life and the more acute the onset the more likely is the organism to resist strenuously. It is a question why this does not also hold true in the mixed Neuroses. One also wonders why age and hospital residence seem to have no significance in the Hysterias whereas they are definitely important in the Mixed Neuroses. The second of these two factors may be related to the fact that the Hysterical patients, showing a more striking and clear-cut clinical picture, are more likely to be kept for a longer time than those classified as Mixed Neuroses, regardless of their response to the treatment. One would expect, of course, that these two factors would be of prognostic value in all the neuroses. The older a person, and the shorter the period of treatment, the less likely the prognosis is to be favorable.

Finally there is the somewhat disconcerting fact that in contrast to the factors presented in table 3 there was a large number of others which showed no significant trends as regards prognosis. These include such important data as heredity, personality, etiologic factors and the various types of symptoms. On closer consideration, however, this is not so surprising. When we compare the factors in table 3 with those just mentioned we find that in the first case we are dealing with data which are essentially more adaptable to objective measurement than are the more subjective factors of personality, etiology or the symptomatology of the neurotic patient. Furthermore, these factors are much more dependent upon the personality of the observer. What may be described by one observer as an "asocial" component in a patient's personality may be described by another as shyness or sensitivity. Similar problems arise in recording etiology or the predominant symptoms. In the case of heredity, too, one must deal with data concerning personality eccentricities or neurotic traits in the patient's family which is obtained from relatives or friends and such data cannot be considered of sufficient reliability to be used in scientific appraisal. When we consider the important role that some of these factors have been found to play in individual cases, it would be logical to suppose that their value as general prognostic indices could also be demonstrated if we could find more objectively valid methods of evaluating them and more suitable standards of measurement and comparison. Until such methods have been devised we shall have to restrict ourselves to the few factors that can be treated objectively.

SUMMARY

Three hundred and forty-one cases of Psychoneurosis, admitted to the Iowa State Psychopathic Hospital during the years 1929–1937 inclusive, were subjected to a follow-up study during the year 1939 and the subsequent course and present

status of these patients is reported here. The studies made of these patients during their stay in the hospital were analyzed in terms of the clinical picture they presented, their life history and the treatment and course in the hospital. The various single factors thus obtained were evaluated in their relationship to the ultimate outcome.

It was found that in the two largest groups (Hysterias and Mixed Neuroses) certain factors stood out as useful prognostic criteria. Intelligence Quotients above 90, duration of the disease of one year or less before admission to the hospital and Permeability Quotients below or above normal value were found more frequently in the cases that recovered than in those who showed no improvement. The method of treatment described as deep exploration resulted in the most frequent recoveries. In addition to these general factors it was found that in the Hysterias, asthenic physical build and gradual onset were most often found in the unimproved cases, whereas the mixed neuroses showed higher age levels and a shorter stay in the hospital among the unimproved patients.

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NEW STUDIES IN MULTIPLE SCLEROSIS, II

Parencephalomyelitis Periaxialis Scleroticans (Acute Multiple Sclerosis) in Various Infectious Diseases

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A RECOLLECTION AND A WISH

It was in the year 1929. The waves of hatred and wrath in the wake of the First World War had just abated, and scientists particularly became active in improving international relations. The idea then arose to have the neurologists of the entire world join in an international congress which would also serve as an instrument for solidifying world peace.

For such a purpose a personality was needed who would combine international fame with energy, tact, and diplomacy; in brief, a man who would possess all the qualities of a great scholar and scientist, in addition to a deep understanding for the great and little weaknesses of man. Such was the need and it was met in the person of Dr. B. Sachs. Everybody who still remembers the first international post-war Neurological Congress in Berne, will recall how this great scientist always found the right way out of misunderstandings and how admirable was his never-ceasing poise.

It is, therefore, understandable that neurologists all over the world join the American neurologists today, on the occasion of the sixtieth anniversary of his activities as a doctor, to thank him not only for his achievements, but also for the creation of the International Neurological Congress. They all have but one wish, that a kind destiny may preserve this worthy life for many more years to come so that, let us hope, in the not too remote future Dr. Sachs, the Honorary President of the International Neurological Congress, may be in a position to revive this useful instrument of international understanding.

—Otto Marburg, M.D.

Encephalomyelitides were observed in close relation to various infectious diseases not usually accompanied by affections of the central nervous system. The nature of this affliction of the nervous system is still under discussion. In some instances the inflammation shows a predominant involvement of the white matter as seen in measles, smallpox, influenza, as well as in postvaccinal sequelae (lyssa, variola, yellow fever). Some of the writers emphasize some similarity of this condition with that of multiple sclerosis. With this in mind, it would seem advisable to use the term *parencephalomyelitis* for these complications to indicate that in this disease there is an accompanying but not a genuine inflammation of the nervous system.

Among the more characteristic pathological changes is the perivascular demyelination particularly around the small veins, with or without preservation of the

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axis cylinders. The glial reaction is usually very marked but varies with the degree of axon degeneration. In instances of severe involvement, with complete destruction of the nerves, the glia is also damaged. This glia reaction was emphasized by Wohlwill (1) as well as by Ferraro and Scheffer (2). In most cases, however, the glia is converted into compound granular corpuscles as macrophages, with glial nodes here and there as an expression of their hyperactivity.

In addition to these alterations in nerve fibers and glia cells, there is a mesodermal reaction consisting of frequent obstructions of the small veins, the importance of which has been recognized by Putnam (3, 4, 41).

The perivenous foci are usually small but sometimes somewhat larger, and their relation to the veins is not always easy to establish. Cases with larger foci are very rare and some writers emphasize their similarity with those in multiple sclerosis. The author collected in the literature such cases which accompanied measles and influenza (infections of the upper respiratory tract), adding some of his own cases.

The aim of this paper is to report exclusively cases of encephalitis accompanying measles and influenza characterized by large foci, and to indicate the nosologic position of these complications and their relation to definite primary affections of the central nervous system.

Table 1 gives a survey of the cases found in the literature.

CASE REPORTS

Case 1. History: A white girl, aged 14 years, had suffered from sore throat with subsequent purulent otitis in early childhood. Before the tenth year of life she acquired measles. The mother of the patient had a chronic, now progressive cerebrospinal disease (encephalomyelitis ?) before childbirth. Four weeks before death the patient had developed sore throat which lasted for fourteen days and was followed by paresthesias and pains in the extremities and a few days later, by weakness of the legs. The examination at this time revealed exaggerated tendon reflexes, ankle clonus, a bilateral Babinski sign, and a very severe disturbance of proprioceptive sensation (astereognosis). All laboratory findings were normal except for a small increase of lymphocytes in the cerebrospinal fluid. The temperature of the patient was elevated. The neurological signs increased in intensity, and drowsiness and somnolence developed a few days before her death.

The course of the disease showed a progressive tendency without remissions. The clinical diagnosis was myelitis.

Histological observations: There is an area of demyelination in the lower cervical segments (C 5–7; fig. 1). In a Weigert preparation a punched out focus occupies the posterior funiculi symmetrically on both sides. A narrow zone of intact nerve fibers forms a seam around the posterior horns except for a small part dorsally on the right side with incomplete demyelination. Within the demyelinated area there are many compound granular corpuscles containing gray-stained debris. In sections impregnated with silver by the Bielschowsky method, numerous axis cylinders are recognized, some swollen but not broken (fig. 2). Evidence of secondary degeneration is absent. In hemalum and eosin preparations (fig. 3) there are some swollen glia cells, well-formed astrocytes with many compound granular cells and glia cells contributing to the perivascular infiltrations. The perivascular infiltrations (fig. 4, A and B) consist of many mononuclear cells with the nuclei being round and densely stained. There are among them cells with brighter nuclei, and a few leucocytes and plasma cells. Compound granular cells in this obviously fresh infiltration are absent, though they are present diffusely in the tissue. Some red thrombi are seen in small veins (right; fig. 3). Near these veins accumulations of glia cells begin to form

TABLE 1

AUTHOR	AGE	SEX	RELATION TO INFECTIOUS DISEASE	PREDISPOSING FACTORS	SIGNS AND SYMPTOMS	COURSE AND DURATION	PATHOLOGICAL FINDINGS
Cramer, A. (5)	19	F	Soon after measles	Alcoholic father	Meningitis with paralysis of legs, bladder and rectum	From Oct. 1879 till Spring 1880 complete recovery. Psychosis (without neurologic signs). End of 1880: schizophrenia?, decubitus, pyemia, exitus, June 1881	Foci of demyelination in the spinal cord around the blood vessels. Many naked axis cylinders, compound granular cells; acute myelitis is diagnosed by the lesion of some axons
Schlesinger, H. (6)	7	M	Beginning of measles during the disease	Father alcoholic; hereditary lues?	Flaccid paralysis of the legs; patellar reflexes absent, ankle jerks exaggerated, positive Babinski sign, skin reflexes absent; priapism; later strabismus, ptosis	Intermittent remittent. Despite scarlatina and diphtheria improvement, then deterioration	Picture resembles multiple sclerosis with mild shadow foci; secondary degeneration and marked infiltration around the blood vessels. Little damage to nerve cells
Brock, J. (7)	6	F	Beginning of measles on fifth day of illness		Sudden rise of temperature, somnolence until death. Spasticity of extremities, ankle clonus, positive Babinski sign, skin reflexes absent; cerebrospinal fluid pressure 290 mm. water, cells, 170, protein increased	Progressive, stupor persistent	Disseminated foci of demyelination around blood vessels, sometimes confluent. Most axis cylinders intact; no mesodermal reaction, none in meninges. Diagnosis of Siegmund (pathologist): encephalomyelitis periaxialis
Mosse, K. (8)	5½	M	Seventh day of illness		Stupor; fixed pupils, flaccid muscles, exaggerated reflexes, later absent; cerebrospinal fluid: protein increased	Death after a few days	Foci of demyelination with compound granular cells and beginning glia increase without any inflammatory changes except for lymphocytic infiltration around one blood vessel
Gagel, O. (9)	8	M	Beginning of measles	Parents degenerated neuropathics	First psychical symptoms, excitability & decrease of intelligence; spastic paretic gait, 9 months later general rigidity, loss of speech, stupor, athetoid movements; disturbance in swallowing	1½ year duration, chronic progressive; pneumonia (terminal)	Multiple foci of demyelination resembling: in the hemispheres diffuse sclerosis; in the lower parts, multiple sclerosis. Compound granular cells, but some plasma cells and lymphocytes (perivascular) symptomatic inflammation; secondary degeneration limited to the pyramidal tracts

TABLE 1—(*Continued*)

AUTHOR	AGE	SEX	RELATION TO INFECTIOUS DISEASE	PREDISPOSING FACTORS	SIGNS AND SYMPTOMS	COURSE AND DURATION	PATHOLOGICAL FINDINGS
Walthard, K. (10)	3	F	6/20 1928 measles exanthema, 6/24 rise of temperature and beginning of nervous signs	Previous pertussis and varicella	Clonism, chorea-athetoid movements	Remittent rise of temperature, deterioration. Duration four weeks	Multiple demyelinations, axon degenerations and slight secondary degeneration; compound granular cells
Sulzer, H. (11)	2yr. 11 mo.	F	At 9 mos. pertussis, chickenpox. Summer 1927 parotitis; 6/17 1928 measles	Grandfather alcoholic	6/17 1928 begin with cold, 6/20 exanthema, 6/22 temperature normal; 6/24 temperature 39.3°C.; coma, with chorea-athetotic movements; strabismus; tonus generally diminished	6/17-7/27 1928	Many foci throughout the brain; demyelination with formation of compound granular cells. Terminal bronchopneumonia
Ferraro, A. (2) and Scheffer, I. H. Case 5	6	M	Seven days after onset of measles (exanthema fading); rise of temperature	Appendectomy 3½ years previously	Drowsiness, headache, coma; temperature 105.6°F.; trismus; conjugate deviation of eyes to the right; slight neck rigidity; knee and abdominal reflexes absent; bilateral Babinski sign; later bilateral ankle clonus	Progressive. 8 days after onset of measles, encephalomyelitis; 15 days later, exitus	Disseminated demyelination with some larger foci (in lumbar segments); perivascular cell accumulations (compound granular cells, microglia, some lymphocytes—rod cells); gliosis of the border zones in the spinal cord
Malamud, N. (12), Case 1	11	M	Measles exanthema; one day later sudden right hemiplegia	Mongolian idiot	Right hemiplegia—first flaccid, later spastic; reflexes exaggerated; right Babinski sign	10/23 1932 onset of cerebral signs; middle of November improvement; 6/6 1937 exitus (miliary tuberculosis)	Many foci of demyelination, some resembling diffuse sclerosis; in the centrum ovale of the frontal lobe, sleeves of demyelination around the veins. Destruction of axis cylinders (lack of secondary degeneration in the internal capsule and peduncle); compound granular cells; progressive glia changes and infiltrations absent
Malamud, N. (12) Case 2	8	M	July 1, 1933 measles, second infection; during convalescence rise of temperature, beginning of cerebral complications	First measles at age of six months; pertussis and varicella	Drowsiness deepening into coma. July 6, 1933, meningeal signs, rigidity of all extremities. Cerebrospinal fluid pressure 207 mm. water, 50 cells per cmm; 41 mg. sugar, 708 mg. chlorides per 100 cc. Coma subsided after blood transfusion, but a hyperkinetic state developed with increased salivation, euphoria, slightly ataxic gait and general incoordination	Remission after blood transfusion. Recovery July 5, 1937 exitus (cause unknown)	Foci of demyelination (corpus callosum) irregularly scattered, perivascular, but also extending from the subependymal region (diffuse). Axis cylinders also destroyed; gliosis; no products of disintegration, no infiltration; only increase in the number of oligodendroglia

TABLE 1—(*Continued*)

AUTHOR	AGE	SEX	RELATION TO INFECTIOUS DISEASE	PREDISPOSING FACTORS	SIGNS AND SYMPTOMS	COURSE AND DURATION	PATHOLOGICAL FINDINGS
Hassin, G. B. (13) and Stone, T. T. Case 1	28	M	Influenza (febrile state) five days; three weeks later onset of signs	?	Numbness left arm, weakness left arm and leg; paresthesias tongue left; followed by complete paralysis left upper and lower extremities; coldness of right side; retention of urine. Signs of hemiplegia of the Brown-Sequard type. Blood: leucocytosis; slight increase of protein in cerebrospinal fluid	Two months duration. Death after laminectomy on the assumption of the presence of a tumor	Demyelination of 3rd and 4th cervical segments with extensive perivascular infiltrations; compound granular cells; increase of microglia in the posterior roots. Axons and myelin sheaths degenerated. Meninges infiltrated by lymphocytes and compound granular cells. Degeneration with inflammation, no secondary degeneration
Hassin, G. B. (13) and Stone, T. T., Case 2	21	F	Influenza and pneumonia two months previously	?	Visual disturbances, drowsiness, right hemiplegia. Temperature elevated. Ross-Jones test + in cerebrospinal fluid, 36 lymphocytes, protein increased. Recovery (June) after typhoid vaccine. Second attack October, difficulty in walking; improvement. Third attack December. Right leg numb and weaker, limp. Vomiting. Paralysis of the lower extremities with exaggerated reflexes and positive Babinski sign, followed by paralysis of the left upper extremity and respiratory disturbances	November, 1938 till 2/6, 1939. Bronchopneumonia	Local demyelination with inflammation (compound granular cells, microglia, lymphocytes, plasma cells); swelling of nerve cells; meningeal infiltration Inflammation pronounced
Greenfield, I. G. (14)	37	M	Influenza two weeks before affection of nervous system		Numbness and flaccid paralysis of legs and lower part of trunk below L_2 on right and L_4 on left. Abdominal reflexes absent, Babinski sign positive, sensation not completely absent. Cerebrospinal fluid: 29 mononuclear cells, protein increased, Pandy reaction positive. Temperature elevated	Progressive five days duration	Perivascular demyelination, increase of cells (lymphocytes, plasma cells, some compound granular cells); karyorrhexis

TABLE 1—(*Concluded*)

AUTHOR	AGE	SEX	RELATION TO INFECTIOUS DISEASE	PREDISPOSING FACTORS	SIGNS AND SYMPTOMS	COURSE AND DURATION	PATHOLOGICAL FINDINGS
Greenfield, I. G. (14)	32	M	Influenza	Alcoholism (30 glasses of beer); indigestion	Flaccid paralysis of the lower extremities, retention of urine, disturbed sensation, abdominal reflexes absent, also tendon reflexes. Cerebrospinal fluid: 16 mononuclear cells, protein increased	Two weeks after onset reflexes present, sensation improved, remittent; seven weeks duration	Demyelination foci *fenestrati* with compound granular, rod and microglia cells. Slight ascending secondary degeneration
Davison, C. (15) and Brock, S.	32	M	Onset of neurological signs on the eighth day of influenza (?)	?	Retention of urine and obstipation; flaccid paralysis of lower extremities; reflexes diminished, abdominal reflexes absent; loss of sensation below L_3 diminished below D_6; Bilateral ptosis, nystagmus, right facial weakness. Proprioceptive sense of lower extremities absent. Left Babinski sign positive. Temperature 100°F. pulse 100. Spinal fluid: protein increase; 80%. polymorphonuclear leucocytes. Blood: 3.1 red cells, 60% hemoglobin, 12.4–18.2 white cells (78–94% polymorphonuclear leucocytes)	Improvement of sensory defects and paralysis after a few days, but urine became sanguinopurulent, sepsis. Exitus. Duration six weeks	Cystopyelonephritis ascendens. Perivascular demyelination in the spinal cord (D 8–10) especially around veins; in patches microglia, astrocytes, and some compound granular cells. Axis cylinders partly or completely destroyed, partly swollen, partly preserved throughout the whole brain
Grinker, R. R. (16) and Bassoe, P.	23	F	Five days after a very severe cold	?	Temperature 99.5°F.; Foot paresthesias; Retention of urine. Two days later disturbances in swallowing, drowsiness, diplopia, vertical nystagmus (?) paresis of palate; speech nasal, swallowing impossible. Coarse action tremor of both hands, paresis lower extremities, right more than left. Knee jerk diminished, ankle jerk absent. Tactile and vibratory sensation on right diminished. Blood: 12,000 leucocytes (80 per cent polymorphonuclears). Cerebrospinal fluid normal	Acute and progressive	Demyelination around the veins with lymphocytic and plasma cell infiltration. Compound granular cells. Axis cylinders destroyed only in old foci, microglia increased in the foci. Meningeal affection

small nodules. In the meninges there is a mild infiltration with leucocytes, lymphocytes, and histiocytes. The meningeal infiltration is not continuous throughout the cord but is represented by discontinuous interrupted areas of involvement. Near the sixth dorsal segment of the spinal cord, there are foci situated dorsally in the distribution of the posterior spinal artery. In the fourth lumbar segment there is a small focus in the left pyramidal tract. The cauda equina shows only hyperemia.

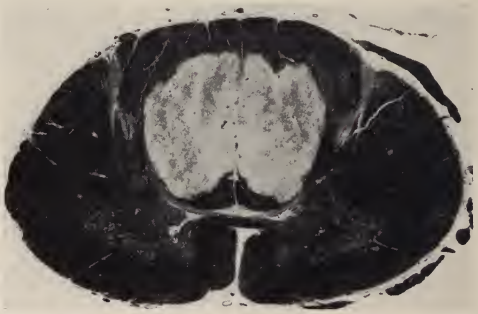

FIG. 1. Case 1., C6, Focus of demyelination (Weigert-Pal stain)

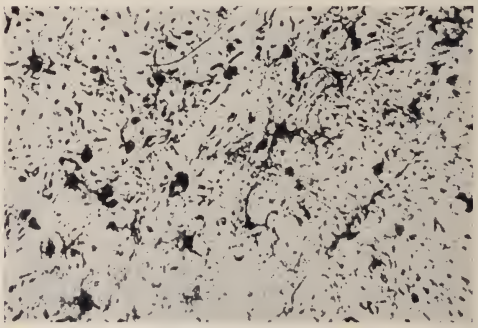

FIG. 2. Case 1. Axis cylinders and incipient ameboidosis in the focus of figure 1 (Bielschowsky stain)

A careful study of the nerve cells reveals most of them to contain normal Nissl bodies. Only a few show swelling, axonal degeneration and shrinking. In some nerve cell nuclei there is marked hyperchromatosis. Some glial nuclei show karyorrhexis.

In the medulla oblongata there are visible some nerve cell alterations in the nature of swellings or shrinking, with some nuclei showing small accumulations of chromatin. There is also some increase of the glia cells, and slight infiltration of the meninges. There is no evidence of secondary degeneration. The pons and midbrain are relatively intact showing only a few perivascular infiltrations. A larger focus of demyelination is found between the

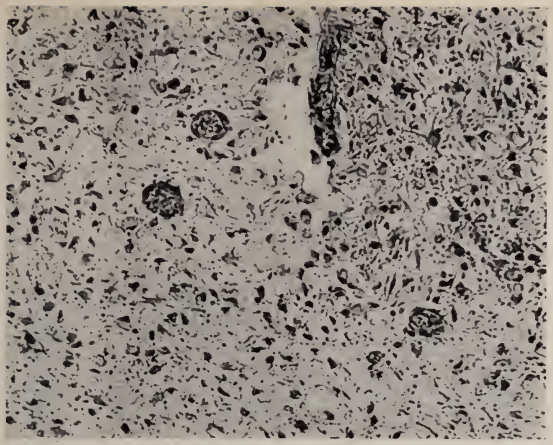

FIG. 3. Case 1. Red thrombi, glia, and compound granular cells in the focus of figure 1 (Hemalum and eosin stain)

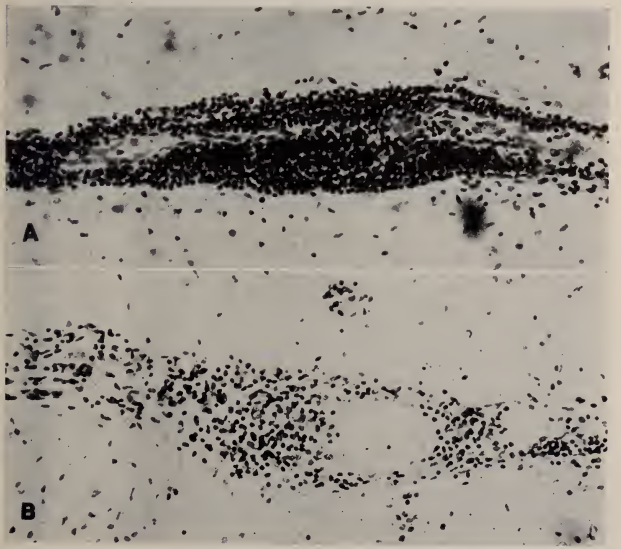

FIG. 4. (A) Case 1. Perivascular infiltration at the border of the focus of figure 1 (Nissl stain). (B) Case 1. Perivenous infiltration within the focus of figure 1 showing the various infiltrating cells (Hemalum and eosin stain).

putamen and the island of Reil in the ventral half of this region. The ventral parts of the external capsule and the insula are demyelinated.

There is extensive edema throughout the cortex cerebri. The nerve cells are widely involved, showing swelling and shrinking. Some of the small veins are thrombosed (red thrombi) without remarkable disintegration of the surrounding tissue. There is discontinuous meningeal infiltration.

Case 2. Measles parencephalomyelitis. A more detailed history was not available. Parts of cerebral cortex, corpus striatum, optic thalamus, cerebellum, and medulla oblongata were studied. The histologic observations are the same throughout these various parts; they may be summarized. There are two types of lesions:

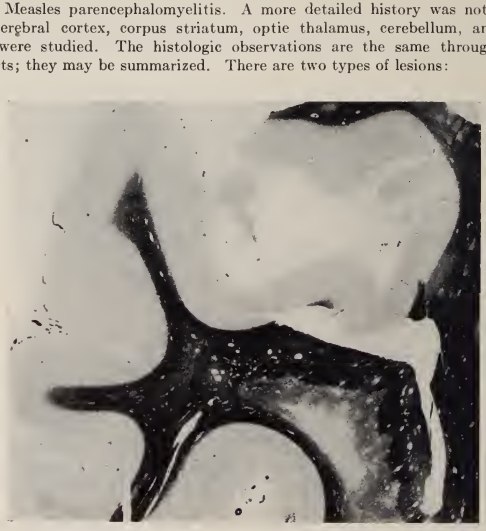

FIG. 5. Case 2. Focus of demyelination in the centrum ovale, frontal lobe, showing differences in the staining of myelin within the focus (Heidenhain stain).

1. Small perivascular disintegrations (demyelinations). As to whether the affected vessels are veins or small arteries is not always possible to determine but the veins seem to be predominantly involved. These lesions show a gradual transition into the normal tissue. While the myelin sheaths have disappeared completely, the axis cylinders have remained intact; some of them, however, are damaged. No secondary degeneration is seen even where there are multiple foci side by side.

2. Larger lesions (fig. 5) without a definite relation to the blood vessels. The demyelination may be complete or in the manner of *Markschattenherde* (myelin-shadow foci). The axis cylinders are present (Bodian staining). The glia reaction in these foci is of two types: compound granular corpuscles are seen in the border zones only near the unaffected region (fig. 6), whereas within the lesion there are fibrillogenetic cells. There is a thick network of fine glia fibrils (incipient sclerosis). The blood vessel walls are usually intact. Swollen intima cells are very rare. Some of the vessels are filled with blood, others show a network of fibrin without any blood corpuscles. Then there are completely closed vessels. As for the distribution of these different vessels, the blood-containing vessels are in zones of normal tissue, the others within the focus. This may serve as evidence of a venous obstruction

(fibrous thrombi); the veins ahead of the thrombus being closed, the vessels behind enlarged. There are also diseased areas with completely normal vessels. Perivascular infiltration is absent in the foci with beginning sclerosis. But in the close proximity of all such foci, the blood vessels show a slight infiltration (fig. 6). The cells lie within interadventitial spaces. The cells are of the compound granular variety mixed with some leucocytes and lymphocytes. These infiltrations are seen throughout the various parts of the nervous system as far as it was examined.

The site of predilection for the several foci is the white matter. That is true especially of the incipient small foci. The larger foci obviously are formed by a fusion of many small foci. Others are rather diffuse giving no clue as to their origin. Sometimes a large, diffuse focus of complete demyelination is surrounded by a seam-like "shadow focus" which helps the recognition of its origin from many perivascular foci. This "shadow focus" is surrounded by a halo of normal tissue and this normal layer is in turn surrounded by many almost fused perivascular foci (fig. 5). Such a focus resembles the concentric focus seen in multiple sclerosis.

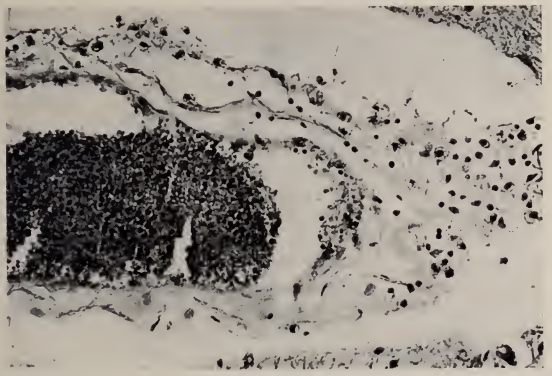

FIG. 6. Case 2. Interadventitial infiltration of a vein outside the focus, compound granular cells (Hemalum and eosin stain).

DISCUSSION

The first question that presents itself is why the nervous system is affected in some infectious diseases (in a very small group of them), while in others under the same conditions the nervous system remains uninvolved. Van Bogaert, Borremans and Couvreur (17) suggest that, in addition to the infection, there must be another predisposing factor to explain occasional involvement of the nervous system: "*L'existence d'une prédisposition familiale vis à vis des séquelles neurologiques et psychiques des exanthèmes infectieux*" may be one of these factors. This explanation had been offered two years before by Sulzer (11) who mentioned trauma as well as preceding infectious diseases as factors capable of destroying the weak resistence of a fragile organism. In this connection the case of Gagel (9) is the only one with a heredodegenerative history. It is difficult to evaluate the significance of the chronic-progressive nervous disease of the patient's

mother in my Case 1 since accurate data are not available. In the cases of Cramer (5) and Schlesinger (6) alcoholism of the parents seems to have served as a predisposing factor, while in Sulzer's (11) case there was alcoholism of the grandfather; hereditary syphilis (?) may have added to alcoholism in Schlesinger's (6) case. Previous infections (measles, chicken pox, pertussis, parotitis, and pharyngitis) are mentioned by Walthard (10), Malamud (12), and Sulzer (11), and were observed in the author's Case 1. Appendectomy $3\frac{1}{2}$ years before the onset of the disease was reported in a case of Ferraro and Scheffer (2) (perhaps a weakening factor); Malamud's (12) Case 1 was a typical Mongolian idiot; and an organic nervous disease of the mother was present in Case 1 of the author. In spite of the small number of such cases and the little attention paid to these predisposing factors, they deserve mention for the influence of such factors is not without significance.

The clinical picture of these types of encephalomyelitides, with the large foci of demyelination (see table 1), is seldom discussed (cf. Boenheim (18), Greenfield (14a), Neal and Appelbaum (19), Ford (20), Rosenheck-Barowsky (21) a.o.). The relation of this herein reported peculiar form of parencephalomyelitis to the infectious diseases it accompanies, is the same as in other forms of accompanying encephalomyelitis with smaller foci. Four to seven days after the onset of measles in close relation to the disappearance of the rash, sometimes before the onset of measles (Malamud, Case 1), the disease of the cerebrospinal axis sets in. In cases with influenza the interval is apparently longer (some weeks to months). Elevation of temperature indicates the beginning of the affection of the nervous system and usually soon disappears though it may last longer in some instances. A repeated elevation of temperature indicates a progression of the brain affection. This repeated rise of temperature and sinking to the normal level a few days later, is characteristic of the picture. There is clinical evidence of multiple lesions in different parts of the nervous system. The presence of many foci is readily recognized, though one of these is sometimes predominant, often concealing the smaller foci. In general, the different clinical pictures are caused by the different sites of the foci. Absence of the abdominal reflexes is a frequent sign as is drowsiness, somnolence, and coma with or without other signs, leading to the false diagnosis of meningitis. The cerebrospinal fluid reveals usually only a slight increase of protein without a corresponding increase in cells; rarely is there a change in the sugar or salt content, thus excluding meningitis. There is occasionally moderate pleocytosis as found in measles (Brock (7), Malamud (12)) and in influenza (Hassin (13), Greenfield (14), Davison-Brock (15)). In Malamud's (12) case this increase of cells was associated with an increase of sugar and salt, contrary to the findings in meningitis. One such case was seen by the author clinically only; the picture closely resembled that of the author's Case 1. Despite the meningeal signs, the cerebrospinal fluid was almost normal. The patient recovered. Notwithstanding the negative findings in the cerebrospinal fluid, there is in almost all cases a meningeal irritation or real meningitis as found on post-mortem examination. It is discontinuous with scanty exudation.

The course is frequently remittent or intermittent (cases of Cramer (5), Schlesinger (6), Walthard (10), Ferraro and Scheffer (2), Malamud (12), Greenfield (14), Davison-Brock (15)). The further progression after a remission is, as mentioned, accompanied by a renewed rise in temperature. The duration of the disease varies from a few days (Ferraro and Scheffer (2)) to more than a year (Cramer (5), Gagel (9)).

The clinical picture resembles that described by the author as acute multiple sclerosis (1906 (22, 23)) and is accepted as such by many writers. This resemblance is true also of the pathologic changes in the affected areas. There is a characteristic discontinuous demyelination with relatively intact axis cylinders and absence of secondary degeneration. In some cases the axis cylinders are swollen or even completely destroyed. But this destruction is limited to a small number of the axons, with lack of secondary degeneration. Rarely, in particular and long-lasting cases (Gagel (9)), does secondary degeneration occur. Whereas in the perivascular demyelination, as in measles, there is a gradual transition into the normal tissue, the large foci in the reported cases are generally punched out as described in acute multiple sclerosis. Sometimes, however, a gradual transition is noted (Mosse-Creutzfeld (8)).

The glia reaction consists of an increase in the smaller elements, particularly the microglia (Wohlwill (1), Ferraro and Scheffer (2)). They remain partly unchanged, partly form compound granular cells. In some cases ameboid glia cells are noted as also seen by the author. These ameboid glia cells are according to Pollak (23a) progressively changed glia cells which in their first stage of phagocytosis show regressive changes. In view of the relatively short duration of the disease, fibrillogenesis is not pronounced but recognizable in the older foci (Mosse and Creutzfeld (8), Sulzer (11), author's Case 1). In some cells (Case 1) there is karyorrhexis as described by Greenfield (14) in influenza, and seen by Perdrau (24) in post-vaccinal encephalitis. The author (25) saw it also in post-vaccinal encephalitis but it is also found in other infectious diseases. In the author's own cases of measles karyorrhexis is absent.

The vascular alterations are of great importance. Putnam (3, 4, 41) drew attention to the changes in the veins, particularly to their thrombosis not only in multiple sclerosis but also in some encephalomyelitides. Indeed, in measles where the onset of the demyelination is very easy to trace, the demyelination develops aroung the small veins as first mentioned by Wohlwill (1). The same is true of some cases of influenza encephalomyelitis (Greenfield (14), Davison-Brock (15), Grinker (16)). It is also true that there are thrombi (red and fibrin thrombi) in these veins causing stasis in the arteries behind the obstruction and a reduction of the lumen in the vessels ahead. The association of this condition with demyelination in measles encephalitis as suggested by Putnam (3, 4), had already been discussed by Lechelle, Bertrand and Fauvert (26) in 1931. These authors assumed the inflammation and not the "stasis infarct" to be the causative factor. In my case there were red and fibrin thrombi within the foci but also in the unchanged tissue. But there were also foci without any thrombosis. Thus the reported cases do not allow conclusions concerning the role of the

thrombi in the process of demyelination. However, one must admit that these phlebothromboses play, though not a deciding, a supporting role in the pathological alterations of the myelin.[2]

Thus the pathologic process as shown in the demyelination, the glia reactions and blood vessel changes, as well as the clinical picture resembles acute multiple sclerosis. It may be remarked parenthetically that in a recent case of acute multiple sclerosis Riser and Geraud (42) found an almost complete occlusion of the small blood vessels by an increase of endothelium cells and fibrous tissue even in regions far distant from the foci. The capillaries remained intact.

Of still greater interest are the perivascular infiltrations. Apart from occasional small hemorrhages (very rare in my cases) there are cells around the small veins different in amount and type, the significance of which varies according to various writers. Occasionally a case is reported without any cells around the vessels (Malamud (12)). In Case 2 of the author there were no infiltrations in the larger foci. But examination of the surrounding tissue revealed compound granular corpuscles and some mononuclear cells within the adventitia and the interadventitial lymph space. The nature of the small round cells is uncertain. But some are lymphocytes while others are leucocytes. These interadventitial cell accumulations are seen to a minor degree throughout the whole brain in the proximity of a focus (also described by Creutzfeld (8) in Mosse's case). The difference between this perivascular infiltration and that in Case 1 of the author is obvious. In the latter case it is easy to differentiate the various cells. In addition to compound granular cells, leucocytes, plasma cells, and some histiocytes, there are many small round cells with dark nuclei and a scanty seam of plasma. These cells are microglia cells as proven by Ferraro and Scheffer (2), whereas Hassin and Stone (13) demonstrated most of the infiltration cells to be compound granular cells. Case 1 of Hassin-Stone (13), and Case 1 of the author show almost the same findings. Creutzfeld (8) found in Mosse's Case 2 in addition to the above mentioned scanty exudation one vessel surrounded by lymphocytes. Thus it seems that in cases of measles the mesodermal reactive exudation is very mild in contrast to that in cases of influenza or so-called influenza. In most of these cases (also in the cases of Hassin and Stone) the meninges are affected showing some exudation like that found in cases of mild meningitis. This discontinuous meningeal involvement more than the perivascular infiltration indicates the character of this process as an inflammatory one.

In view of the various findings, such as lack of infiltration with few cells surrounding the veins, or a rather massive infiltration, it is understandable that there is no agreement as to which category the several cases may belong. Since the demyelination is the most striking change, it is usually assumed that there is a degenerative process called "encephalomyelosis" by Sulzer, and "multiple degenerative softenings" by Hassin and Stone (13), the infiltration being only

[2] I discussed this subject in my paper "Studies in the pathology and pathogenesis of multiple sclerosis with special reference to phlebothrombosis and Guiraud's bodies," J. Neuropath. & Exper. Neurol., 1: 3–13, 1942.

symptomatic in the opinion of Spielmeyer (27). The latter view is out of accord with the existence of infiltrations throughout the whole nervous system including the meninges. There are those who call such cases "acute multiple sclerosis" (Grinker (16)). It seems of advantage to avoid a specific classification for the cases herein reported and to speak merely of "reactions" as stressed by Putnam and Alexander (28). Of these reactive processes there are four kinds:

1) Reaction of the white substance consisting of a discontinuous demyelination with relative intactness of the axis cylinders and absence of secondary degeneration.

2) Reaction of the glia, a predominantly progressive change with formation of compound granular corpuscles, an increased number of microglia cells, and formation of glia nodules, with some regressive glial reactions (ameboid glia formation).

3) Vascular reaction—phlebothrombosis in part responsible for the demyelination, and exudation, so-called encephalomyelitic reaction, with perivascular infiltrations predominantly around the smaller veins.

4) Reaction of the meninges—a discontinuous mild inflammation.

Each of these reactions may vary in intensity, extent, and sometimes in the severity as expressed by an accompanying degeneration of the axis cylinders. These variations depend in part on the type of the infection. In measles the process is relatively mild. But there are such cases with severe disintegrations, for example Gagel's (9) case, in which the long duration may have been the cause.

Concerning the glia reaction, the variations in the several cases are far greater. Perhaps the investigations of Lotmar (29), dysentery-toxin inflammations produced artificially, give an explanation. There were two different kinds of reactions accompanying similar lesions in the parenchyma. One was progressive, forming compound granular cells, the other regressive with formation of ameboid glia. Both these reactions could be produced by the same dosage of the toxin. Thus one has to assume an individual factor causing these differences, if one does not like to assume a constellative chance factor. This individual factor which was mentioned in man by Sulzer (11), and also van Bogaert, Borremans, and Couvreur (17), may either be a hereditary or an accidental one (trauma, previous infection, concomitant diseases). It leads to diminished resistance of the organism thus predisposing to grave changes. With these facts in mind, it is quite possible that the cases with simple demyelination, intact axis cylinders, and formation of compound granular cells may be caused by the same agent as the cases with severe changes and ameboid glia.

The vascular reactions in their various forms are more difficult to explain. Since the blood-vessel walls are generally normal, the formation of thrombi depends on an endogenous factor. It is a matter of fact that, as Loeb (30) demonstrated, some infections produce thrombi (staphylococci, for instance) as accepted by Tannenberg and Fischer-Wasels (31). But there are many other causes which might be responsible for this remarkable occurrence (platelet destruction, changes in the chemical constitution of the blood, for instance; Hoefer, Putnam, Grey (41)). In close relation to the thrombi is the character of the

infiltration. The complete absence of any infiltration is unlikely; there are at least compound granular cells and some blood cells or some glia elements within the adventitial space. One reason for the differences in the amount of the exudation was found by Binz (32). Such exudation is assumed possible only in the presence of a well-ventilated blood vessel in addition to some other factors. The oxygen content in the small veins is less than the content in the arteries ($\frac{2}{3}$). The occasional obstruction of the small veins is another oxygen-decreasing factor. The investigations of Lewy and Thorner (33), on artificial deprivation of oxygen, support the views of Binz (32). There are found severe damages to the parenchyma, lesions in the blood-vessel walls, small hemorrhages, but never an exudation. In some cases a complicating severe infectious disease may cause a greater extension of infiltration as shown by Moore and McCordock (34) who described a case in which a hemorrhagic virus pneumonia complicated measles. This is evidence that exudation depends not only on the type or intensity of the infection but also on other circumstances.

One of the aims of this paper is to demonstrate the great resemblance of the reported cases in their clinical and pathological features to those of acute multiple sclerosis, or as it was termed by me, *encephalomyelitis periaxialis scleroticans*. The latter disease was described by me as characterized by an acute demyelination with relative intactness of the axons, and absence of secondary degeneration; progressive reaction of the glia forming compound granular cells and filling the periaxial gaps by glia fibrils (sclerosis); and accompanied by an inflammatory vascular reaction including thromboses.

Since this morbid entity is a primary disease and is often in close relation to various infectious diseases, this latter type may be called *parencephalomyelitis periaxialis scleroticans* thus emphasizing the similarity with acute multiple sclerosis despite the presence of certain deviations. This does not exclude the probability that some other form of encephalomyelitis may also accompany various infectious diseases. Steiner seems justified in objecting to the use of the term multiple sclerosis in all cases of demyelination. But there is no evidence that Steiner's (35) recently published case under the name of "homophasic cerebrospinal demyelinating periangiosis" represents a specific morbid entity. For the patient had suffered multiple traumatic lesions and it is well known that such lesions occasionally cause perivascular demyelinations (contusion) at a great distance from the site of the trauma. This was shown experimentally by Helfand (36) in Ferraro's laboratory.

The causes of these cerebrospinal complications have not yet been revealed. Certain, however, is that the causative agent spreads into the tissue by way of the small veins producing demyelination and some reactions of glia and blood vessels. There are many theories to explain this fact (Hurst (37)) but it seems that only experimental investigations can lead to an understanding of this peculiar process. Lotmar's respective paper on dysenteric toxin encephalomyelitis was mentioned above. To this may be added the investigations of Claude (37a), and the more striking experiments of Putnam (38) and his co-workers (39) with tetanus toxin. These investigations as well as the different vaccinia encephalitides seem to bear

evidence that bacterial toxins are responsible for the complications in the neuraxis. Since different toxins have the same or almost the same effect, one has to assume in the different toxins a common factor, the nature of which has not yet been revealed.

Putnam's (3) view that the link in all these demyelinations may be phlebothrombosis, is difficult to prove in the reported cases since they were not investigated sufficiently in this respect. When assumed as the common factor some toxic agent that spreads by way of the veins, one has to refer to Shwartzman's (40) investigations which demonstrated a phenomenon of local tissue reactivity by the use of sterile bacterial filtrates. This reaction is generally assumed to be due to antigenic toxins, and is similar in many instances to spontaneous infectious lesions. Thus the reported cases may be due to a similar mechanism.[3]

SUMMARY

Cases of encephalomyelitis are reviewed and added to the author's own cases, which developed in the course of some infectious diseases (measles, influenza), and resembled acute multiple sclerosis.

Acute multiple sclerosis (encephalomyelitis periaxialis scleroticans) is an acute demyelination with relative intactness of the axis cylinders and absence of secondary degenerations, a progressive reaction of the glia (compound granular cells and fibrillogenesis), and an inflammatory reaction of the mesoderm.

Since the reported cases resemble clinically as well as pathologically the above described picture, they are called by the author parencephalomyelitis periaxialis scleroticans ("para", to express the accompanying encephalomyelitis) forming a particular morbid entity. Its cause has not yet been revealed but one might conclude that there is a reaction in brain similar to that elicited by Shwartzman with sterile bacterial toxins.

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THE INCIDENCE OF THE VARIOUS TYPES OF HEART DISEASE. A POST MORTEM STUDY

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Considerable difference exists in the literature concerning the relative incidence of the various types of heart disease (1–7). This is due in part to geographical factors, but the variation in the percentages cited is too great to be explained on this basis alone. In addition, many writers (8–11) maintain that coronary artery sclerosis and occlusion are steadily increasing in frequency. Much of the confusion is a result of the multiplicity of cardiac nomenclatures used and the retention of numerous obsolete terms. The majority of published statistical analyses collected from death certificates are unacceptable because they are tabulated in accordance with the International List of the Causes of Death and the Manual of Joint Causes of Death (12). In these coronary artery disease has only recently been separated from other heart diseases and coronary occlusion even now does not form a distinct group. Furthermore, certain cardiac diseases are incorrectly given preference over others as the cause of death. For example, death is attributed to "myocarditis" when it appears on the death certificate in association with coronary occlusion, although surely the latter is the cause of death.

We have attacked the problem of classification by studying all the cases examined at necropsy at The Mount Sinai Hospital in which death was caused by heart disease. The type of heart disease was recorded in each case; when more than one type was present, only the one directly resulting in death was noted. We have confined ourselves to post-mortem material because the clinical diagnosis may be incorrect; this is particularly true of coronary artery occlusion in which minute microscopic examination is often essential.

The census of The Mount Sinai Hospital wards is representative of the general population. There are 176 adult male beds and 162 adult female beds, and 111 beds for children up to twelve years. Thus three-fourths of the patients are adults. The period covered by this survey was 1917 to 1938 inclusive, the data being collected for each year. During this time there has been a gradual rise in the average age of patients; the average age at death was 28 years in 1917 and 47 years in 1938. This was to be expected since the life span is gradually being lengthened (13).

In table I it is seen that during the period 1917 to 1938 the total number of autopsied persons in whom death was caused by heart disease increased with the increase in all hospital admissions, but that the percentage of such cases in the entire autopsy material changed little, the average being 15 per cent. It is slightly higher at present.

We have grouped heart disease for the purposes of this communication as follows: coronary artery occlusion, coronary artery disease without occlusion, acute and chronic rheumatic, luetic, congenital, subacute bacterial endocarditis,

TABLE I

Annual incidence of cardiac deaths in autopsied cases, 1917 to 1938

YEAR	AUTOPSIES	TOTAL HEART DEATHS	
		Number	Per cent
1917	261	16	6
1918	182	19	10
1919	172	21	12
1920	143	17	12
1921	280	25	9
1922	318	23	7
1923	288	58	20
1924	330	33	10
1925	381	55	15
1926	350	60	17
1927	423	68	16
1928	461	61	13
1929	530	53	10
1930	494	65	13
1931	579	65	11
1932	568	77	13
1933	433	66	15
1934	380	51	13
1935	371	54	14
1936	395	17	18
1937	389	108	27
1938	450	70	15

TABLE II

Incidence of various types of heart disease in cardiac deaths in autopsied cases, 1917 to 1938

YEAR	TOTAL NO. OF CASES	CORONARY ARTERY DISEASE			RHEUMATIC HEART DISEASE	LUETIC HEART DISEASE	CONGENITAL HEART DISEASE	SUBACUTE BACTERIAL ENDOCARDITIS	MISCELLANEOUS
		Acute occlusion	Chronic	Total					
		per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
1917	16	13	7	20	56	0	0	24	0
1918	19	5	10	15	53	5	10	16	0
1919	21	5	10	15	55	5	5	20	0
1920	17	0	18	18	48	3	0	13	18
1921	25	12	16	28	40	4	4	24	0
1922	23	21	9	30	43	4	4	0	19
1923	58	3	28	31	36	5	5	12	10
1924	33	9	21	30	36	12	0	15	6
1925	55	11	20	31	37	5	5	17	5
1926	60	7	37	44	31	8	4	8	5
1927	68	9	18	27	47	9	6	7	4
1928	61	11	19	30	42	8	6	8	6
1929	53	11	11	22	41	7	6	17	6
1930	65	15	20	35	32	5	3	14	10
1931	65	18	24	42	42	2	3	5	5
1932	77	20	28	48	20	7	5	12	9
1933	66	24	18	42	29	3	5	9	12
1934	51	26	12	38	26	4	4	8	20
1935	54	43	17	60	31	0	0	9	0
1936	70	30	10	40	34	3	6	13	4
1937	108	30	16	46	32	2	4	8	8
1938	70	46	16	62	24	2	2	7	2

and miscellaneous types including acute and chronic *cor pulmonale*, acute bacterial endocarditis, Fiedler's myocarditis, beri-beri heart, etc.

Although the total number of cardiac deaths up to 1925 was small and, therefore, the percentages obtained less significant than those for the later years, it is clear (table II) that there has been a definite change in the relative incidence of the types of heart disease encountered. Prior to 1920 more than half the cardiac deaths occurred in rheumatic heart disease and less than 20 per cent in coronary artery disease; coronary artery occlusion was reported rarely. Subacute bacterial endocarditis was common, probably because of the particular

TABLE III

Incidence of various types of heart disease in relation to total number of autopsies, 1917 to 1938

YEAR	AUTOPSIES	TOTAL CARDIAC	CORONARY OCCLUSION	CORONARY SCLEROSIS	RHEUMATIC-LUETIC		CONGENITAL HEART DISEASE	SUBACUTE BACTERIAL ENDOCARDITIS	MISCELLANEOUS
					Heart disease	Heart disease			
		per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
1917	261	6	.8	.4	3.4	0	0	1.5	0
1918	182	10	.6	1.2	6.0	.6	.2	1.8	0
1919	172	12	.6	1.2	7.2	.6	.6	2.4	0
1920	143	12	0	2.0	3.3	1.4	0	3.4	2.0
1921	280	9	1.2	1.6	4.0	.4	.4	1.4	0
1922	318	7	1.6	.6	3.3	.3	.3	0	1.2
1923	288	20	.7	5.6	7.0	2.2	1.2	2.7	2.4
1924	330	10	.9	2.0	3.7	1.2	0	1.5	.6
1925	381	15	1.6	2.9	5.2	.8	.8	2.4	.8
1926	350	17	1.2	6.4	5.5	1.5	.6	1.5	.9
1927	423	16	1.5	3.0	7.7	1.5	1.0	1.2	.7
1928	461	13	1.5	2.6	5.6	.9	.9	.9	.9
1929	530	10	1.1	1.1	4.2	.8	.6	1.8	.6
1930	494	13	2.0	2.6	4.2	.6	.4	1.8	1.4
1931	579	11	2.0	2.0	4.0	.2	1.0	1.1	1.1
1932	568	13	2.6	3.9	2.6	.9	.7	1.5	1.2
1933	433	15	3.7	2.8	4.8	.5	.7	1.4	2.0
1934	380	13	3.4	1.6	3.4	.5	.5	1.0	2.9
1935	371	14	6.2	1.6	4.9	0	0	1.4	.5
1936	395	18	5.3	1.8	6	.5	1.0	2.4	.8
1937	389	27	8.5	2.3	9.3	1.5	1.0	2.0	2.0
1938	450	15	7.0	2.4	4.2	.2	.2	1.1	.2

interest in this disease in this hospital at that time (14). Between 1920 and 1930 there was a drop in the relative incidence of rheumatic heart disease to 40 to 45 per cent, and a rise in coronary artery disease, including coronary artery occlusion. Since 1930, and especially 1935, the relative increase in coronary occlusion has been pronounced. In 1938 it accounted for 46 per cent of cardiac deaths whereas there was a fall in the incidence of coronary artery disease without occlusion and a further drop in rheumatic heart disease which caused less than one-third of the deaths. Thus there has been a progressive increase in the relative incidence of deaths due to involvement of the coronary

arteries, chiefly occlusive, and a progressive fall in those due to rheumatic heart disease. Other writers have found a similar trend (15, 16). It is pertinent that in the last six years particular attention has been paid by us to the search for coronary artery occlusion in the pathologic examination of specimens; the routine procedure employed was that of making cross sections of each vessel at intervals of several millimeters and performing microscopic examinations in every case.

There has been a decrease in the incidence of luetic heart disease and of subacute bacterial endocarditis, which is probably explained by a change in the type of patient admitted to the hospital in recent years. There has been considerable variation in the incidence of cases in the group of miscellaneous heart disease but the higher percentages were attained in the years when the total number of cases was small and therefore may not be significant.

In Table III is shown the incidence of the various types of fatal heart disease in relation to the total autopsy material. This table also shows the distinct rise in incidence of coronary artery occlusion, especially since 1935. There is seen a slight increase in that of coronary artery disease without occlusion. The incidence of rheumatic heart disease has not increased materially and that of luetic heart disease and of subacute bacterial endocarditis has fallen slightly.

DISCUSSION

Our findings indicate that since 1935 coronary artery disease, especially coronary occlusion, has been the chief cardiac cause of death, accounting for almost two-thirds of cardiac fatalities. In 1938 coronary artery occlusion was found in 46 per cent of cardiac deaths, outnumbering rheumatic heart disease almost 2:1. Coronary sclerosis without occlusion was next most common, forming 16 per cent of the total. Before 1925, on the other hand, one-half the deaths occurred in rheumatic heart disease and less than one-third in coronary artery disease, coronary occlusion being rare. Thus a relative rise in incidence of coronary artery disease, chiefly occlusion, has occurred which can be adequately explained in two ways. The first is the increasing span of life resulting from the reduced incidence and mortality of infectious disease at all ages, and from the general improvement in nutrition and hygiene. Thus, the number of persons reaching middle and old age is steadily increasing; in 1935 24.6 per cent of the population was over 45 years of age in contrast to only 17.7 per cent in 1900 (13). The increase in expectation of life since 1900 is equal to that of the previous 100 years (17). In our series of cardiac patients the average age at death rose from 28 years in 1917 to 47 years in 1939. Consequently, the absolute as well as relative incidence of coronary artery disease is greater at the present time. The second explanation is the increased accuracy in diagnosis, especially of coronary artery occlusion. This holds true pathologically as well as clinically. It will be remembered that in our series there has been a sharp rise in the tabulated incidence of coronary artery occlusion since 1935. This year marked the innovation of a special pathologic routine designed to detect all increases of occlusion. Unless a painstaking search is made, coronary occlusion may be

easily missed. Thus, reexamination of a number of hearts studied prior to 1935 disclosed a considerable number of occlusions previously overlooked. In spite of contrary views expressed by a number of authors (8–11) we believe that the actual incidence of coronary artery occlusion in each age group is no greater now than in former years; that is, under similar conditions of pathologic examination, just as much coronary artery disease would have been found among persons 50 to 60 years old in 1900 as in an identical group at the present time (18).

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POTENTIAL OR LATENT CONGESTIVE FAILURE IN THE AGED

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Usually pronounced left cardiac failure is heralded by an obvious cause, commonly prolonged hypertension, coronary disease or valvular disease. My purpose in this report is to call attention to lesser grades of left cardiac failure to which no apparent cause can be assigned except advanced age, and in which the clinical evidences are so mild that they mimic other maladies, notably, upper respiratory infections or mild bronchopneumonia and chronic bronchitis. It is obvious that the recognition of such cases is important from the standpoint of therapy. With the exception of a passing comment by Fishberg (1), this syndrome has apparently not been recognized.

CASE REPORTS

Case 1. History. T. K., aged 70, a widow. Her previous history was entirely irrelevant. The patient had always been a highly emotional, nervous person, and a poor sleeper; she had been taking various coal tar hypnotics with little effect. She impressed one as having the hyperthyroid temperament, but her basal metabolic rate was normal. She had suffered from a persistent thirst for years and drank excessive quantities of water. No cause for the thirst was discoverable; there was no evidence of diabetes mellitus or diabetes insipidus and she was not addicted to salty foods. In July 1940, she consulted a physician for a cough of a few months' duration. He diagnosed an upper respiratory infection but treatment brought no relief. Toward the end of the summer, the cough disappeared spontaneously. The cough reappeared at the end of November and she consulted me on December 15. The cough was nocturnal and there was a small amount of mucoid expectoration. Her temperature was 99°F. She had slight exertion dyspnea, but no precordial oppression.

Examination. The patient had no excessive fat. The pulse rate was 86 and was regular. The apex beat of the heart was in the sixth space in the nipple line; there was no murmur and the second aortic sound was accentuated. The blood pressure was 200 systolic and 105 diastolic. There were a few moist râles at both lung bases. Fluoroscopic examination of her chest showed no widening of the cardiac shadow to the left or right and the aortic knob was consistent with her age. The electrocardiogram showed only a left ventricular preponderance. The liver and spleen were not enlarged. The urine had a specific gravity of 1.024 and was free of albumin and glucose. There was no peripheral edema.

Course: She was placed on a salt poor diet. The fluids were restricted to 1000 cc. a day and ammonium chloride gr. 22½ was administered three times daily. At the same time, 1 cc. of Mercupurin was injected into the buttock. Four days later, the cough had practically ceased. She had lost 2¼ pounds in weight as the result of diuresis. Her blood pressure had fallen to 155 systolic and 95 diastolic, and accentuation of the second aortic sound and the basal râles were no longer present. One week later the cough had completely disappeared. The blood pressure was 150 systolic and 88 diastolic. During the succeeding months the same regimen was continued but no mercurial diuretic was given after the initial dose. At her last observation (May 12, 1941) she felt perfectly well. The blood pressure was 140 systolic and 80 diastolic.

Summary. A woman, aged 70, highstrung and emotional and an excessive water drinker had no obvious cardiac disorder. The only evidence of left cardiac failure was a persistent nocturnal cough with slight exertional dyspnea and moist râles at both pulmonary bases. The elevated blood pressure found on one occasion may be ascribed to congestion (*Stau-*

ungshochdruck). Under the conventional treatment for left cardiac failure, all evidences promptly and completely disappeared. There was no doubt that her excessive fluid intake disturbed the cardiovascular compensatory mechanism resulting in left-sided cardiac failure.

Case 2. History. A. H., aged 70, a widow. About 40 years ago, this patient suffered from a bronchopneumonia. Since then she had had a slight hacking cough without expectoration. She had been drinking about a quart of fluid daily.

Examination: There were fine moist râles at the right base. The heart was normal in size, and the apex beat was in the fifth space, nipple line. The blood pressure was 140 systolic and 80 diastolic. The cardiac sounds revealed no abnormality. Fluoroscopy of the chest revealed nothing abnormal in the heart and the aortic knob was consistent with her age. The electrocardiogram showed a left ventricular preponderance; T_3 was inverted; the fourth lead was normal. The liver and spleen were not enlarged. There was no pretibial edema. The urine was free of albumin and glucose. In April, 1940, she complained of some oppression in the chest on walking and slight dyspnea on bending over. The blood pressure was 180 systolic and 85 diastolic. In June 1940, she complained of slight dyspnea on exertion and slight nocturia. The blood pressure was 165 systolic and 85 diastolic. The urine showed a faint trace of albumin. The liver was just palpable below the free border of the ribs and there was slight pretibial edema. In February 1941, she developed a severe cough, almost entirely nocturnal, with moderate mucoid expectoration, and dyspnea on exertion. The blood pressure was 170 systolic and 85 diastolic. There was slight edema of the shins. The liver could not be palpated. The urine showed a slight trace of albumin. Fluoroscopy of the chest showed no change from the previous findings. She was placed on the conventional regimen for left-sided cardiac failure, namely, a salt poor diet, restricted fluids, ammonium chloride gr. 22½ three times daily and 1 cc. of Mercupurin was injected into the buttock. Following this injection, she developed severe cramps in the legs and lost 4½ pounds in the succeeding 24 hours. The cough and dyspnea abated almost completely and she felt well until May 21, 1941 when the cough and dyspnea returned. The blood pressure was 175 systolic and 85 diastolic. She was placed on the same regimen as before. On this occasion she received only ½ cc. of Mercupurin in the buttock. She again suffered from leg cramps and in the succeeding 24 hours she lost 2½ pounds. The cough and dyspnea were again completely relieved. At present, she is taking a maintenance dose of digitalis (1½ cat units) daily and feels perfectly well. The blood pressure remains around 140 systolic and 70 diastolic. The urine is free of albumin and glucose and the pretibial edema has completely disappeared.

Summary. A woman, aged 70, with a "dry" bronchiectasis at the right base resulting from a previous bronchopneumonia developed two attacks of mild left cardiac failure without any apparent exciting cause. The moderate hypertension during the attacks may be interpreted as due to congestive failure (*Stauungshochdruck*). Between attacks, the blood pressure was perfectly normal. Under the conventional therapy, the attacks of congestive failure were promptly relieved. The severe cramps in the legs during Mercupurin diureses may be attributed to the rapid loss of chlorides. The slight swelling of the liver and the pretibial edema indicated that, in all probability, this patient also had some degree of right-sided cardiac failure.

Case 3. History. Mrs. S., aged 65, a widow. This patient had suffered from attacks of biliary colic for many years. Finally, after a severe attack with clinical evidences of obstruction of the cystic duct, a cholecystectomy was performed by Dr. A. A. Berg in October, 1939, which was followed by complete recovery. She remained well until February 29, 1940, when she presented herself because of some dyspnea on exertion. She had gained 10 pounds during the past year and had slight nocturia.

Examination: There were no positive findings in the chest; the heart was not enlarged either by percussion or by fluoroscopy, the apex beat was in the fifth space, and in the nipple

line, the sounds were pure and there was no accentuation of the basal sounds. The blood pressure was 130 systolic and 75 diastolic. The liver and spleen were not enlarged. There was pretibial edema. The urine showed a specific gravity of 1.026 and was free of albumin and glucose. She weighed 160 pounds, a considerable increase for her height and age. The electrocardiogram showed only a left ventricular preponderance and notched P waves. There was a regular sinus rhythm, rate 76 per minute.

Course: She was placed on a low calory diet. On March 27, 1941, she presented herself with the history of a persistent cough associated with "music in the throat" at night, with slight mucoid expectoration of six weeks' duration. The cough was mostly nocturnal and prevented sleep. There was slight nocturnal dyspnea as well. She was in the habit of drinking 5 cups of coffee daily in addition to other fluids including a much advertised carbonated drink. Physical examination revealed no change in the cardiac status. The blood pressure was 124 systolic and 70 diastolic. There were a few moist râles at both pulmonary bases. She weighed 159 pounds. Her temperature was 98.2°F. The urine was clear. She was ordered a restricted intake of fluids without carbonated drinks, a salt poor diet and ammonium chloride gr. 22½, three times daily. Two days later, the cough had practically ceased and she had lost four pounds in weight. The râles at the lung bases had completely disappeared. About three weeks later, the nocturnal cough returned but under the same regimen and the addition of two cat units of digitalis daily and an occasional injection of 1 cc. of Mercupurin, the cough and dyspnea disappeared completely.

Summary. A woman, aged 65, who had undergone cholecystectomy for obstruction of the cystic duct one year previously, developed a nocturnal cough with some mucoid expectoration and slight dyspnea. Cardiac examination revealed nothing significant; the blood pressure was normal. There were noted a few basal pulmonary râles. Following the conventional treatment for congestive failure, the nocturnal cough, dyspnea and basal râles, disappeared completely.

DISCUSSION

The observation in private practice within a short period of time of three cases of congestive failure without obvious cause except the age of the patient suggests that such cases are by no means uncommon. It is easy to appreciate how readily the diagnosis may be overlooked in favor of an upper respiratory tract infection or chronic bronchitis. Left-sided cardiac failure from which these patients suffered, is typically manifested by nocturnal asthma with marked dyspnea and orthopnea, cyanosis, aggravated restlessness, cough with mucoid or bloody expectoration, tachycardia and thready pulse, oliguria, and cold sweat; but these manifestations were witnessed in these patients in a highly attenuated form. The only symptoms were cough which was largely nocturnal and associated with little or no expectoration, and slight exertional and nocturnal dyspnea. The only significant sign was the presence of moist basal pulmonary râles. Occasionally, the systemic blood pressure was raised during the attack (*Stauungshochdruck*).

It seemed hardly necessary to make special studies of the circulation (e.g., saccharin time, ether time, venous pressure) to confirm the diagnosis in these patients. The diagnosis was clinically obvious without such tests and the diagnosis was confirmed by the almost immediate response to therapeutic diuresis.

In the absence of persistent hypertension and of any valvular defect, the possibility that these patients may have underlying coronary disease with arteriosclerosis of the decrescent type of Allbutt must be seriously considered as the

cause of their congestive failure despite the absence of anginoid distress or manifest electrocardiographic evidence. Arteriosclerosis of the coronary vessels is almost the rule in aged folk. Moreover, it is a familiar observation that advanced coronary disease even with marked narrowing of the coronary vessels may be found at post-mortem examination without previous clinical evidence.

There is one other morbid anatomic change that must be considered, namely, brown atrophy. According to Fishberg (1), brown atrophy is merely an accentuation of the physiologic deposition of pigment that begins in the first decade of life. Under ordinary circumstances, brown atrophy of the cardiac muscle has no clinical significance; whatever insufficiency of muscular function this lesion entails is compensated by the diminished physical activity that comes with advancing age. However, it can be readily understood that any undue strain, whatever its nature, may uncover the reduced efficiency of a musculature thus affected.

Whatever the anatomic background may be, it is clear that a profound functional change has been engendered in these cases and that the compensatory cardiovascular mechanisms have been thrown out of balance. In other words, the balance between the nutritive requirements of the cardiac musculature and its available blood supply has been seriously disturbed.

It is unnecessary to enter into a discussion of the physiologic mechanisms brought into play by the existence of left-sided cardiac failure. These have been admirably detailed by Fishberg (1). The chief problem in these cases is rather the nature of the inciting factors which directly initiate these phenomena.

A number of possibilities exist. Physical strain as an incitant of congestive failure is a familiar clinical observation. The strain necessary to upset the compensatory balance in a patient with latent or potential failure becomes progressively less with time. For this reason exercise tolerance tests sometimes give valuable information.

Acute infections often bring to light latent congestive failure. This is a different problem from that of congestive failure following rheumatic fever or diphtheria which cause serious anatomic changes in the myocardium. It concerns rather the comparatively mild upper respiratory infections, or mild attacks of bronchopneumonia, which in some as yet undemonstrated way upset the compensatory balance. The failure is as apt to occur during convalescence as during the febrile period, and practically always manifests itself in patients in the twilight years. In the young it occurs only in those with previously damaged hearts.

Sudden emotional stresses are well known instigators of congestive failure in potential cardiac patients. Attacks of failure frequently follow a terrible dream or frustrated sexual excitation. Attacks following coitus probably are ascribable to both emotional and physical factors. A fixed anxiety or a dreaded anticipation is another common inciting factor. The emotional factor accounts in a large part for the predominantly nocturnal incidence of the attacks.

There is, I believe, one other cause whose importance is not sufficiently appreciated. I refer to excessive intake of fluids. This seems to have been the

factor in two of my patients. Restriction of fluids is probably the most important therapeutic recommendation at our command in the alleviation and prevention of congestive failure. When cardiac reserve is maintained at a fairly high level, this measure alone, suffices to keep the patient free from attacks. Salt restriction also diminishes thirst and with the employment of mercurial diuretics, removes the latent and manifest edema brought on in part by an unnecessarily high fluid intake. These measures are therefore important adjuvants. The mechanism whereby edema initiates congestive failure is, in all probability, related to an increase in blood volume with resultant embarrassment of the left ventricle. Particularly noxious are carbonated waters. This is well understood when we consider that diuresis is best maintained when the pH of the blood is well toward the acid side, in the achievement of which the ammonium salts prove a sovereign remedy. I have repeatedly observed that when a mercurial diuretic is given without the expected result, the patient has been previously alkalinized by either carbonated water, bicarbonate of soda, a magnesium salt or a saline diuretic. In potential congestive failure, therefore, their use should be avoided.

SUMMARY

Left-sided cardiac failure may occur in elderly patients without clinically manifest evidences of either prolonged hypertension, coronary disease or valvular defects. They present potential or latent congestive failure. The possibility that these patients have underlying coronary disease cannot be excluded even in the absence of angina. Another possible anatomic background is brown atrophy of the myocardium. The clinical evidences of congestive failure may be represented in a very attenuated form in contrast to the pronounced types and may consist merely in a cough, mostly nocturnal, with little or no mucoid expectoration, and with slight exertional and nocturnal dyspnea, moist râles at the pulmonary bases and occasionally, elevation of the blood pressure during the attack (*Stauungshochdruck*). These clinical evidences simulate upper respiratory infections, "chronic bronchitis", and mild bronchopneumonia, but they respond promptly to the conventional therapeutic measures for congestive failure. The possible inciting causes for attacks of left-sided cardiac failure are discussed. In two of the three cases reported, excessive fluid intake was in all probability the cause, and in one case its evil effect was aggravated by the ingestion of carbonated waters.

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THE BISEXUALITY OF MAN[1]

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By sexuality is meant those personality factors which are separable from reproduction and heredity, although at all times intimately linked with them. Thus, the capacity to manufacture an egg is one phase of sex—the reproductive phase. The creature that manufactures the egg has as a sum total of its drives and inhibitions a female sexuality which may be more or less normally organized. The power to manufacture sperms which are capable of fertilizing the egg is male reproductivity, but the drives and personality traits which urge the male to seek or not to seek the female and which give him his outward characteristics make up the male sexuality. Thus, the capacity to manufacture eggs need not be conjoined with complete female personality as, for example, when a female homosexual becomes pregnant; or, when a male homosexual, experimenting with heterosexuality, impregnates a woman, demonstrating that the seed still retains the power of fertilizing a female egg, although the individual himself does not ordinarily seek females and may show very definite feministic traits. An original hermaphroditic nature in man has become lost in the shuffle of evolution, but there still remains a bisexuality which is the most important of all the sexual phenomena that can be separated from essential reproduction itself (1, 2).

We might recapitulate at this point those facts of embryology which give a structural basis for this bisexuality. The characteristics of maleness or femaleness are related to the predominance in development of either the Müllerian duct in the female or the Wolffian body in the male (3). These go on to form the primary structures of sex, although in each sex there remain residual organs of the opposite sex. Moreover, only the primary organs of sex develop from the Müllerian duct and the Wolffian body, which is different from the case of the secondary sexual organs, the external organs of generation. The male and the female structures which externally proclaim sex develop from the same structure, the genital ridge. Under the influence of hormones of appropriate type and involving probably an interplay between male and female hormones there is differentiated in the female the labia majora and minora, the clitoris and the vagina, whereas in the male a particular hormonic stimulation is responsible for the specific differentiation of the penis and scrotum and for the descent of the testicles into the scrotum. The breasts of the male, which have no secretory function, proclaim the residual femaleness of the man. Anomalies in development of these external organs and structures probably spring from anomalies in the quantity and quality of male and female differentiating hormones.

In addition to the specialized primary organs of sex, the external genitalia, and the breasts, there are certain derivative characteristics which are probably

[1] From the Division of Psychiatric Research, Boston State Hospital, Boston, Mass., aided by grants from the Commonwealth of Massachusetts and the Charlton Research Fund, Tufts College Medical School.

of great importance in the development of the sexual personality. The typical female of the human species is shorter than her mate, and the body-form is notably different. Differences exist also in certain bony parts. Moreover the different relative amounts of subcutaneous adipose tissue and of somatic musculature have not been given the attention they deserve. We believe that these may be related to differences in the amounts of cholesterol and creatinine in the blood, and in later papers we shall discuss this relationship. There are other essential physico-chemical phenomena which are related to maleness and femaleness. The female has a proportionately lower metabolic rate and, in addition, usually has fewer red blood cells per cubic millimeter of blood. Thus it appears that plenty of scope exists for variation in the comparative physical, chemical, anthropological, and psychological-instinctive reactions of men and women (4).

All the sexual hormones are 17-keto-steroids and thus, whether their evolution is into estrogens (5) or androgens (6), they are closely allied in their chemical structure. Moreover, estrogenic substances have a profound influence on the sexual organs of the male sex, and androgens have been used experimentally and clinically for their effects on the female sexual organs (7). The influence of androgens is not exclusively, but only predominantly in the direction of maleness and the estrogens are predominantly, but not exclusively female hormones. Furthermore, androgens and estrogens are both present in each sex in human beings. Accordingly, the difference between the two sexes can be reduced essentially to the matter of quantitative differences in the manufacture and excretion of both hormones resulting in the dominance of one over the other (8).

In view of the fact that colorimetric methods (9) were employed in determining the urinary excretion of hormonal substances in the present study, several disabilities and errors must be mentioned at this point. In the female the product of the ovary, estradiol, and in the male the product of the testes, testosterone, are not excreted in the urine at all and so escape measurement and evaluation by this or by any other technique. Moreover, there are other 17-keto-steroids in the urine which may represent no active sexual function whatever. By these tests alone it is, therefore, impossible to distinguish between the urine of a male and a female.

Some of these difficulties may be related to the fact that the urine is an excretion and constitutes an end-product of metabolism. It is true that no one has as yet been able to set up a precise and definite standard of normality so far as the urine of human beings is concerned, or, at any rate, to express in exact figures the normal range of human hormonology. We shall await precise, yet practical tests for hormones in urine, blood and tissue extracts which will give us an adequate and complete hormonic picture of sexual personality (10). However, it has happened often in the history of medicine that clinical facts of importance have been established even by markedly imperfect methods. With these reservations we therefore offer the results of this study.

During the evolution of this research there developed points of view about autoeroticism, homosexuality and heterosexuality which were not taken into account during the actual work but which, we believe, deserve a few remarks.

Autocroticism, it appears to us, takes three main forms: 1) As seen in very young children and in certain psychopathic individuals, and especially in those who have inferiority feelings, anxiety, depression and anhedonia, it is a form of excitement-seeking from one's own organism, which is not fundamentally sexual but which can be called sensual stimulation as a relief from adverse feeling. It can be compared to that anhedonic eating which one sees in people who have no real appetite for food but who seek pleasure by this form of visceral stimulation, and especially when depressed, harassed, or agitated. 2) Masturbation may be

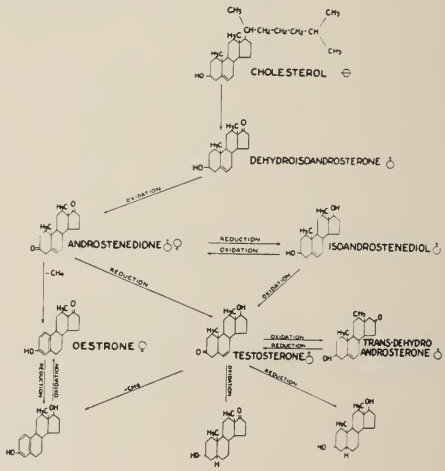

CHART I. Chemical relationship of cholesterol and various sex hormones
The structural formulae and derivation are shown of some of the more important 17-keto-steroids having male and female sex hormone potency. Some of these substances are synthetic and are not known to occur in the human body, and others which are actually present cannot be extracted from biological materials.

merely a substitute for heterosexuality, where the opposite sex is not accessible or where there is lacking either opportunity or drive. 3) In some of our cases, it has been a substitute for homosexuality, and the technique may even mimic this phase of sexuality, as when there is manipulation of the rectum or of the breasts, and where the fantasy is homosexual.

Homosexuality itself is no unitary phenomenon having constant biological or psychological value. It varies quite markedly from time to time, from place to place, and from individual to individual. Thus, so far as time and place are concerned, homosexuality had a high standing in the Greece of classical times, although it is entirely a *subrosa* practice in the Greece of today and in most of

the world. Those who are particularly interested are referred to the famous paper by Burton in the last volume of his edition of the Arabian Nights. Even in a community like ours, male homosexuality, with which we are mainly concerned, and with which our material deals, has varying psychologic and biologic aspects. We turn, therefore, to male homosexuality and kindred matters.

MATERIAL, GROUP CLASSIFICATIONS AND METHOD

Our material consists of 85 cases in which the question of homosexuality was raised. These were derived from 1) private practice, 2) individuals incarcerated at the Massachusetts State Reformatory in Concord, 3) individuals who had reported at a university department of hygiene, and 4) individuals suspected of, or showing, some homosexual conduct at the various state or private mental institutions.

Group I: A man may be heterosexual yet through cultural, economic and environmental pressure become homosexual. Thus, in jails and schools there is no access to women. Some heterosexual males take on homosexuality, although they discontinue its practice when the opportunity for heterosexuality returns. For economic reasons certain low-grade individuals may become active or passive participants in homosexuality just as other criminals steal or murder. These individuals may be classified as sexually polymorphous, since even under extreme economic or social pressure, most males do not become homosexual.

Group II: Another type of homosexuality is presented by those individuals who are fundamentally incapable of heterosexual relationships, yet who have no real homosexual drive, but who are sought out by active homosexuals and find a certain social pleasure and profit in the relationship.

Group III: There are individuals who are at first heterosexual and who develop homosexuality as a phase of altered development not easily understood but representing a shift in sexual personality rather than a transitory experimental phase.

Group IV: There is the true homosexual who from the earliest days of his life has strongly desired and preferred relationship with the male, who may in his strivings for normality try heterosexuality and, in certain cases, even marry. However, he is never fundamentally potent, his cravings, fantasies, desires and drives are homosexual, he falls in love with members of his own sex, and acts towards other men and boys as a lover, or at least becomes sexually excited by them, and is, generally speaking, cold, indifferent, or even repelled by the female. Such an individual is not necessarily of the "fairy" type, and in fact, he may be quite masculine in appearance. It is probable that our studies at the present time are not detailed enough to uncover the physical anthropology of maleness and femaleness, or to reach real conclusions as to the correspondence between outward form and inner drive.

Group V: Into this group we have placed those paradoxical or atypical cases in which there is pathologic sexuality (frigidity and impotence), but, so far as we could discover, no true male homosexuality, yet in whom the hormonology had the same general pattern as that of the true male homosexual.

Because of lack of space, we shall cite only typical cases of the five groups outlined above, realizing fully that our cases are classified with difficulty.

A few preliminary statements are necessary. First, the amounts of the androgens are stated in international units per twenty-four hour volume of urine (i.u./d) and then translated into *gamma* for comparison with amounts excreted of the estrogens. The ratio between male and female substances is as important as the absolute amount of male and female substances present. Thus, a normal ratio between male and female hormone in a man is from 4:1 to 6:1. Where the ratio is about 3:1, there is generally, although not invariably, true male homosexuality. Ratios between 3:1 and 4:1 merely suggest the essential homo-

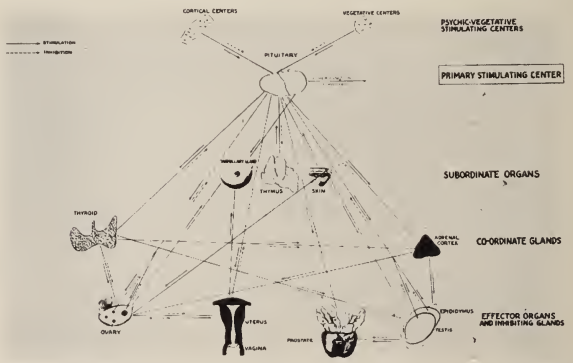

CHART II. Physiological relationship of glands and organs to sex hormone formation The multiplicity of organs concerned with the formation of sexual hormones is shown together with the role each organ plays in the formation of these hormones. Contrary to widespread belief, the ovary and the testis are not the main sites of formation of sex hormones, but only elements in a chain consisting of at least ten links. The great variety of organs concerned with sex hormone formation makes it easily understood why a seemingly confusing variety of abnormal hormonal conditions can occur and why similar abnormalities of hormonal states may have a quite different meaning clinically.

sexuality of the individual. A large absolute amount of the female hormone, likewise brings up at least the question of male homosexuality, irrespective of the ratio

CASE REPORTS

Group I, polymorphous group

Concord Case 2, S. S., aged 28, single. Sexual life predominantly heterosexual in experience and desire. A passively acquiescent homosexual with socially important individuals for financial gain. Physical findings: somewhat effeminate movements but masculine body build. Hormone findings: androgens 160 i.u. (16,000 gamma), estrogens 3,900 gamma. Ratio about 4.5:1.0.

Concord Case 23, W. W., aged 33, single. Criminal record: larceny and robbery. Sexual life essentially heterosexual; homosexual activities within the jail. Asthenic physical type, genitalia small. Hormone findings: androgens 126 i.u. (12,600 gamma), estrogens, 3,900. A low androgen content for his age; female rather moderately high, both within normal limits. Ratio 3.5:1.0.

Group II, adynamic sexuality, passively homosexual

Concord Case 3, C. M., aged 28, single. Criminal record: sodomy and robbery. (Sodomy in Massachusetts means any kind of aberrant sexual activity.) The social history indicates that all his sexual drives are low; that his homosexuality is passive. Physical findings: atrophy of right testicle, a gracile boyish build with effeminate mannerisms and gestures. Hormone findings; androgens 55 i.u. (5,500 gamma), estrogens 1,500 gamma. Ratio about 4.5:1.0. With so low an androgen content, there is great liability to error in the tests, but there is certainly an extremely deficient hormonal excretion. The estrogens are also low for a male of his age, the normal being around 3,000 gamma.

Concord Case 5, J. I., aged 20, single. Criminal record: sodomy and robbery. The clinical history is that of lowered drive in both directions with some homosexual and some heterosexual desire, but with very little heterosexual conduct. Physical findings show a generally undeveloped and immature physique. Hormone level: androgens 92 i.u. (9,200 gamma), estrogens 2,000 gamma. Ratio 4.5:1.0. The androgen level, however, is very low for a man of his age; the estrogens are also diminished.

Concord Case 12, J. McD., aged 28, single. Criminal record: sodomy and larceny. Sexual life: no heterosexual desire, mutual masturbation with boys. Physical findings: asthenic configuration of trunk, scanty pubic hair, a generally dysplastic individual. Hormone findings: androgens 110 i.u. (11,000 gamma); estrogens 3,700 gamma. Ratio 3.5:1.0. Since mutual masturbation can be defined as an activity to be carried on without high sexual desire, it is difficult to state whether this should be classified as homosexuality or mutual autoeroticism.

Group III, heterosexuality followed by exclusive homosexuality

We have two very interesting cases in which sexuality becomes reversed and in which the hormone findings are mutually contradictory.

Hospital Case 1, G. L., aged 65, married. During the earlier part of his life, he was heterosexual, married, had children. After the age of forty, he developed a mental disease in which there was most conspicuous a savage homosexual drive so that he assaulted and attempted to use sexually young boys and even young men. He was committed to a private mental hospital and their records state that he makes attacks on male attendants and shows a ferocity in the homosexual direction. Hormone findings: androgens 360 i.u. (36,000 gamma), estrogens 12,000+ gamma. This case is unique in our experience, first, because there is an extremely high amount of androgens—far beyond what one would expect at sixty-five, and very high even for a man of twenty-five; secondly, there is also an extremely high female hormone. There is thus an original heterosexuality which was replaced in middle life by homosexuality. The hormone study is, on the whole, consistent with the clinical history.

Concord Case 27, F. D., aged 31, married. Criminal record: sodomy and larceny. A psychopathic personality of dull intelligence. He was heterosexual from the age of eighteen to twenty-six, married, and had one child. He turned homosexual after marriage and has preferred active homosexuality since. Physical findings: general body form is masculine; there is some kyphosis; testes are small; cutis marmorata. Hormone findings: androgens

169 i.u. (16,900 gamma), estrogens 1,800 gamma, which is quite low. The ratio is about 9:1, which is very high. We are unable to explain these hormone findings which are quite inconsistent with those reported in the previous case.

Group IV, true male homosexuals

The true male homosexual represents our largest group and the one most intensively studied by us. In general the following statements may be made: These individuals range clinically from 1) those who have homosexual cravings and seek medical help, never having yielded to their desires; 2) those who have had homosexual relationships but who feel troubled by their abnormality and also seek medical attention and advice (these two groups coming mainly from private practice and a university department of hygiene); 3) those who have yielded to their desire and drive, who have been arrested for homosexual conduct, and who have not, on the whole, sought medical advice. Our material in this group is so rich as to make selection of cases difficult.

University Case 7, A. A., aged 20, single, college student, intelligent, conscious of homosexual desires since early childhood. He has been an active homosexual since the age of sixteen. School medical examination shows a very good-looking boy with slight feminine characteristics. Hormone findings before treatment: androgens 131 i.u. (13,100 gamma), estrogens 9,633 gamma. Ratio 1.5:1. This urine is very strongly characteristic of the true male homosexual. There is a low androgen content for a person of his years and an excessive amount of female hormone. Following treatment by injections of testosterone, he stated that his fantasies changed and he now has heterosexual desire. Hormone findings following treatment: androgens 238 i.u. (23,800 gamma), estrogens 6,710. Ratio about 3.5:1. While the female level is still high, the male hormone is now normal for his age. (We may state at this point that our results with injections of hormonal products have not been consistent or in general encouraging.)

University Case 9, K. R., aged 19, single, college student, with strong homosexual trends, attracted by the virile type of male, who finds the masculine body very alluring, and has no sexual drive towards girls or women, although he has had occasional heterosexual dreams. Physical structure masculine; he is interested in art, music and the drama. It is stated that the "general psychometric pattern resembles that of the female, although the differentiations are not clear enough to make much of it. There is nothing quantitative in the present responses to suggest homosexuality and although the qualitative picture in the Rorschach and word association is abnormal, there is no experience to associate it specifically with the type of instinctive situation reported" (i.e., homosexual). Hormone findings: androgens 184 i.u. (18,400 gamma), estrogens 6,080 gamma. Ratio 3:1. This represents a relatively low normal male level and a high female level. We regard him as a true homosexual, sufficiently inhibited so that there is an inner struggle with no overt homosexual acts.

Case 9,381, G. J., aged 37, single, a lawyer, of very good social position who received much psychiatric treatment for years both for homosexuality and for an associated neurosis. The neurosis has not disabled him. He has continued to work at his profession and has associated himself with many social movements of consequence in the community. He became conscious of his homosexual trends early in life. These were associated with love of decoration, a desire to arrange flowers, an avoidance of games involving physical contact, a preference for tennis in which he excelled. His attraction towards males was the first sign he had of any conscious homosexuality at the age of fourteen or fifteen. He had homosexual relationships, especially intracrural or face-to-face, without fellatio which repelled

him although he submitted to it on a few occasions. He made many attempts at heterosexual relationships but these failed because the erection was partial and the orgasm premature or absent. He has been attracted to women, mostly from the social standpoint, and wishes desperately to get married. He has reached his present age, however, without any affair culminating in successful sexual relationships. His body form is slender and masculine, although on the whole somewhat under-muscled. Hormone findings before treatment: androgens 140 i.u. (14,000 gamma) which is relatively low, estrogens 5,600 gamma. Ratio of 2.5:1. He has had considerable psychotherapy and of late has been given androgenic substances, following which the hormone findings showed: androgens 231 i.u. (23,100 gamma), estrogens 3,465 gamma. Ratio 6+:1. This would be a very normal formula, but unfortunately this urine was examined during the time of the hormonie treatment. Actually, there has been no fundamental change in sexual drive or desire.

University Case 3, B. J., aged 25, single, college student. It is interesting to note that in many of our university cases the specimen was first examined and diagnosis reached without either seeing the individual or his clinical history. This is a typical case. Hormone findings: androgens 135 i.u. (13,500 gamma), estrogens 4,408 gamma. We reported to the university that this represented a ratio of 3:1; that this man was probably homosexual in desire, but was not engaging in homosexual conduct, as the balance on the whole was nearer normality than in the homosexual. The institutional authorities then reported that this was an accurate diagnosis of the situation; that the man had no heterosexual drive; that he had resisted actual homosexual conduct; and that he had consulted the institution's clinic because of the abnormal homosexual drive. Physical findings: short, not muscular; hair distribution normal; no outstanding stigmata except the general lack of muscular development and a general softness of voice and manner best described as over-refinement. He was placed on injections of testosterone. A month after treatment was begun hormone findings showed androgens 171 i.u. (17,100 gamma), estrogens 3,300 gamma, representing a rise in the male hormones, and a reduction on the female side. Ratio 5.5:1. Following treatment the patient stated that his fantasies were now heterosexual although he had engaged in no heterosexual activity; the homosexual fantasies were not marked. In this case there seems to be a correspondence in the changed hormonic value following treatment and an altered sexual personality.

Case 12,379, S. I., aged 29, single, accountant. Earliest sexual satisfaction achieved by auto-homosexuality, in other words, by rectal manipulation. Later heterosexual attempts were made frequently, but he was never potent. Homosexual fantasies were very marked, although there was no overt homosexual conduct. Rectal manipulation still continues. This self-manipulation is a sort of thwarted homosexuality. Hormone findings: androgens 202 i.u. (20,200 gamma), estrogens 9,400 gamma. The androgen value is normal for his years, the estrogens very high. The ratio is less than 2.5:1. We regard him as a true homosexual although he may be classed as polymorphous. His heterosexuality, however, is a concession to his desire to be normal, since he has little or no real heterosexual drive.

The above are typical cases of the true male homosexual and in the great majority of our cases the clinical features and the hormonology have at least a rough correspondence.

Group V, paradoxical group

That one cannot make a diagnosis on the basis of the hormone findings alone is shown by this group of paradoxical cases. There are twelve cases in this series, the main characteristics of which are the following: Nine individuals are single, three are married and have children. Two types of sexual aberration are present: 1) where the individual is entirely continent and has not attempted either

heterosexual or homosexual relations; 2) where the individual, whether single or married, has been fundamentally impotent, that is, there has been only a partial erection and *ejaculatio procox* or no ejaculation whatever. Hormonologically this group is characterized by what appears to be a homosexual urine, in that there is usually either an average or low amount of male hormone present and an excessive amount of female hormone, the ratio being about 3:1 or even less. It would seem that in this group there was a balance which led nowhere, so to speak, from the point of view of any potent sexual direction.

Case 12,296, H. C., aged 43, business man, married, two children. His personality has been characterized by lack of drive in all directions. He procrastinates in any business venture to the point of failure, and although he is entirely honest, he never looks after his bills with any efficiency. Although with good original ability, he has gradually declined in the social-financial scale, despite the fact that he is industrious when set to a job. Sexually, he has never given his wife satisfaction, and this has been much more completely the case in the last five years. There is partial erection with either no or a very slight discharge. The body form is fatty rather than muscular and there is a general softness physically and apparently psychologically. Hormone findings: androgens 138 i.u. (13,800 gamma), estrogens 6,465 gamma. The ratio is about 2+:1. The male hormone level is relatively low, the female level is definitely high.

Case 12,174, O. W., aged 37, single, professional man, who had become a drug habituee using barbiturates to excess, never to the point of intoxication but to the point where his efficiency was impaired because of long mornings spent in bed. He is one of six siblings, *none of whom has married*. He is an intelligent man with no active psychosis. Sexually he claims to be entirely virginal so that he has never had sexual desire and has had very few autoerotic experiences. He has never fallen in love and has had no social-sexual relationships with women. There are no homosexual trends. Body form is not strikingly deviate. Hormone findings: androgens 178 i.u. (17,800 gamma), estrogens 7,410 gamma. The ratio is 2.5:1. The male hormone level is adequate for his age, the female level is definitely high.

Case 11,920, C. M., aged 35, single, clerk, with a very definite retreating character, with feelings of inferiority and a general sense of incapacity to match his personality against others, who developed an anxiety state of severe grade. Sexual life: he has had very definite oral paresthesiae associated with sexual desire. In addition, in his early years he masturbated somewhat, although not excessively. He has attempted heterosexual relationships but has always failed, there being an imperfect erection and precocious discharge. He feels extremely debilitated when he has sexual desire, with a paresthesia of peculiar type starting from his genitalia and involving his body as a whole. There are no homosexual trends. The general physique is inferior, flabby, and he is an overgentle, quiet and refined type of man. Hormone findings before treatment: androgens 200 i.u. (2,000 gamma), estrogens 7,700 gamma. The ratio is about 2.66:1. The male hormones are adequate in amount, the estrogens are very definitely high. He received oreton by mouth, following which the hormone findings were androgens 170 i.u. (17,000 gamma), estrogens 2,950 gamma. Despite this marked change in hormone level, there has been no change in sexual potency or general sexual drive.

Case 11,376, W. A., aged 42, married, professional man. Patient has been known to one of us since his college days. There has always been anxiety, a sense of inferiority, with considerable conflict about sexual life. He has married and has two children. Nevertheless, he has never been fully potent. The erections have been insufficient and of short duration. He has never given his wife satisfaction, and the ejaculation is usually quite precocious. From time to time he falls into a marked state of depression with threats of suicide. He has undergone much psychiatric and psychotherapeutic treatment, as well as

drug therapy, with no avail. Body form is relatively masculine, although he has always been non-aggressive physically. Hormone findings: androgens 98 i.u. (9,800 gamma), which is definitely low; estrogens 4,500 gamma which is on the high side and somewhat beyond the normal for males, the ratio being about 2+:1.

DISCUSSION

There is no question that, although the reproductive apparatus itself usually is sharply unisexual, man is bisexual. That is to say, male and female hormones are present in each individual in varied ratios with marked individual fluctuations in the ratio between male and female hormones excreted in the urine.

The establishment of a standard ratio is difficult, and we do not pretend that we have reached anything more than a rough approximation to such a standard. Deviation from that standard is roughly linked with alterations in the sexual personality, especially as measured in terms of male and female drive.

Homosexual conduct, as we conceive it, may arise from various sources. We have cited 1) a group in which the individual is mainly heterosexual depending on opportunity and various environmental circumstances, but who becomes homosexual when excluded from heterosexual conduct. We call this group polymorphous. 2) In a second group the individual is low in all drives, takes up homosexuality in a passive way, the homosexuality in reality being a sort of mutual masturbation or a complaisance without the drive of the true homosexual. This group is characterized by low male and female hormone excretion. 3) A third group shows an alternation from heterosexuality to homosexuality. The hormonal relationships here are not clear, since in one case described the hormone value was exceedingly high in both directions, and in the other case it was low on the female side. 4) A fourth group constitutes what we call the true male homosexual, who is excessively or predominantly homosexual in drive, conduct and fantasy. In this connection we point out that there is such a state as autohomosexuality in which body manipulation, reminiscent of homosexual attention, takes place in the form of anal manipulation. This group is characterized by a hormonal formula which runs true to expectation in most of the cases, although there is an occasional exception. The male hormone level in the urine is usually low, or it may be average. The female hormone level is disproportionately high. The ratio between the male and female hormone level is altered in the direction of 3:1 (as measured by gammas) or may be even lower. 5) Finally, we have described a paradoxical group, essentially impotent or without drive, whose urinary hormonal values are distinctly homosexual, as measured by our formula, but who show no homosexuality. As an explanation, which is purely speculative, we state that there is a neutralizing balance between male and female hormones which does not permit virility and which may even nullify desire.

The chemical tests utilized are relatively crude. It is known that essential hormones, such as testosterone and estradiol, are not present as such in the urine and furthermore, that some of the 17-keto-steroids which are evaluated by the androgen and estrogen tests are not necessarily sexual hormones. Taking all these errors and difficulties into account, there nevertheless remain important clinical correlations between the sexual constitution of a male and the hormonal values established by the examination of his urine for androgens and estrogens.

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THE REGENERATIVE CAPACITIES OF NERVE AND MUSCLE*

An Experimental Study of the Factors Causing Faulty Recovery of the Neuro-Muscular Mechanism

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The variations in the functional recovery of muscles following injuries to the peripheral nerves innervating them has long been recognized in surgical practice. This variation has frequently been ascribed to the differences in the regenerative power of the nerves involved, a view well summarized in the statement of Dean Lewis[1] who classified the nerves in the order of their regenerative power as follows:

1. Musculocutaneous
2. Radial
3. Internal popliteal
4. Median
5. External popliteal
6. Ulnar.

Although such a classification has considerable justification in that it is of some practical value, its emphasis upon the variation in the regenerative capacity of nerves would appear to be unwarranted by a closer analysis of the factors involved. Since, clinically, motor recovery is judged by the strength of the regenerating muscles, it is necessary to consider, in addition to the possibility of variation in the regeneration of nerves, such factors as: a) the length of the nerves or rather the relative remoteness of the muscles to be reinnervated; b) the size of the muscles reinnervated; c) the number and grouping of the reinnervated muscles which are involved in single actions and functionally tested; and d) the mechanical advantage from the standpoint of leverage of the muscles reinnervated.

Such an analysis shows: 1) that the musculocutaneous nerve innervates large powerful muscles situated in the arm with good mechanical leverage to accomplish the single action of flexion of the forearm; 2) that the radial nerve supplies strong muscles a little more distally with good mechanical leverage and unified actions of extension at the elbow, wrist and fingers in addition to supination; 3) that the internal popliteal nerve innervates the large and powerful calf muscles whose leverage is excellent and whose chief action is plantar flexion of the foot; 4) that the median nerve supplies numerous smaller muscles of the forearm and hand with a leverage only fair to good in the action of pronation, flexion of the wrist, fingers, etc.; 5) that the external popliteal (common peroneal) nerve supplies the muscles of various sizes on the anterior and lateral aspects of the leg, whose mechanical leverage ranges from only fair to good and whose action is divided, the dorsiflexion of the foot and toes being opposed by the peroneous longus and brevis, also innervated by the external popliteal nerve; and 6) that

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[1] Lewis, D.: Principles of Peripheral Nerve Surgery. J. A. M. A., 75: 73-77, 1920.

the ulnar nerve supplies the more distal muscles of the forearm and hand which possess only fair to good leverage and the secondary action of assisting in the flexion of the wrist and finer movements of the hand. From such an analysis it is evident that even though the nerves regenerated equally well, the other factors considered would explain at least in large part the variations in the return of function which have been observed clinically in the neuro-muscular units considered.

As has been implied in this analysis, the neuro-muscular mechanism forms a physiological unit which can be judged clinically only by the power and action of the muscle component and, when proper recovery fails to occur, one cannot be certain which component of the neuro-muscular mechanism is at fault. Following injuries to peripheral nerves, all parts of the neuro-muscular mechanism degenerate. Specifically, the structures involved are the nerve fibers peripheral to the injury, the motor end-organs, and the innervated muscle fibers. The usual assumption that the nerve is at fault when proper recovery fails to occur is based upon the fact that the nerve is the structure which was injured. As may be seen from this analysis, however, such an assumption is not warranted, since a failure of regeneration on the part of any one of the component structures forming the neuro-muscular mechanism could equally well explain the failure of recovery as observed clinically following injuries to peripheral nerves. In fact, ruling out post-traumatic cicatrization, which ordinarily is done by exploratory procedures and neurolyses, it is reasonable to assume that the failure of recovery is due to that component of the neuro-muscular mechanism which is least capable of regeneration. Although numerous studies have been done on the degeneration and regeneration of nerves, of muscles and to a less extent of motor end-organs, apparently no correlated study on all three component parts of the neuro-muscular mechanism has been done with the object of evaluating their relative powers of regeneration, or of determining which component possesses the least capacity of regeneration. Because such knowledge is essential to a proper understanding of the factors involved in the recovery from injuries to peripheral nerves, the experimental studies described below were undertaken with the hope of obtaining critical evidence on this important problem.

METHOD

In order to make a correlated study, on experimental animals, of the nerve endings, end-organs and muscle fibers in all stages of degeneration and regeneration, biopsies of muscle taken at intervals were necessary. A muscle of considerable size and extent was required, so that repeated biopsies would be possible without earlier biopsies disturbing the nerve or vascular supply to subsequent ones. To avoid complications in the skin, which are likely to develop with a consequent impairment of sensory supply and which might make a series of successful biopsies difficult or impossible, an unmixed motor nerve was required. It was essential, furthermore, to select a nerve of sufficient size and accessibility to permit satisfactory surgical manipulation.

The thoracodorsalis nerve and the latissimus dorsi muscle of the dog met these requirements. The latissimus dorsi muscle in the dog is the large triangular muscle of the back, running from its fascial attachments along the spinal column and the lumbo-dorsal fascia upward and laterally into the apex of the axilla. The muscle is thick in the axilla but fans out into a thin sheet-like structure which lies directly below the skin of the mid-back. It is supplied by the thoracodorsalis nerve, which enters the muscle inferiorly near its insertion high in the axilla and divides into numerous branches which follow the course of the muscle fibers from a superior-anterior to an inferior-posterior direction. Repeated biopsies on the muscle are possible and, if done in an orderly fashion through parallel incisions starting above the level of the twelfth rib and subsequently through similar incisions at progressively higher levels, the earlier biopsies need not interrupt the nerve supply to the later ones. The thoracodorsalis nerve may be readily isolated in the axilla. It can be identified following faradic stimulation by the characteristic contracture of the latissimus dorsi which adducts and extends the humerus.

The procedure consisted of 1) severing the thoracodorsalis nerve in the axilla, 2) observing the progressive degenerative changes of the nerve endings, the end-organs and the muscle fibers in the latissimus dorsi muscle by means of periodic biopsies, 3) resuturing the thoracodorsalis nerve at varying periods following its ligation and 4) observing the regenerative changes in the aforementioned structures by means of a further series of biopsies on the latissimus dorsi muscle.

Preliminary studies on several dogs showed that simple cutting of the thoracodorsalis nerve, suturing strips of muscle between its ends or burying the proximal end in neighboring muscles did not entirely prevent neural regeneration and the reinnervation of the latissimus dorsi muscle. The remarkable regenerative powers of this nerve in the dog thus made it impossible, by the foregoing methods, to control the experiment, that is, to sustain the degenerative process over known and controllable periods. This difficulty was finally overcome by simple ligation of the nerve with heavy corded silk. The ligature was tightened sufficiently to produce a physiological block as indicated by the failure of response to faradic stimulation, but was not drawn so tight as to cut the sheath of the nerve. Thus, as proved by subsequent pathologic examination, a local cicatrization was produced which completely severed the neural supply to the muscle, and the nerve fibers were so trapped in their sheath and the cicatrizing process at the site of the ligature that regeneration was prevented.

In resuturing the nerve, the cicatrized portion was resected and fresh ends in good condition were anastomosed by two or three arterial silk sutures through the nerve sheath.

Control biopsies of muscle were obtained at the beginning of each experiment and at intervals of two weeks during the period of degeneration, except in those experiments in which this period lasted three months or longer. In these longer degenerative periods biopsies were taken at monthly intervals. In six experiments a biopsy was obtained two weeks following the anastomosis of the nerve; a second biopsy was taken three weeks later and monthly biopsies were

secured thereafter. In the remaining experiments, monthly biopsies were taken throughout the period of regeneration. In three experiments the nerve was anastomosed one month after its severance. Two experiments were performed for degenerative periods of two months and three months each. Single experiments for degenerative periods of four and six months also were done. In one dog the thoracodorsalis nerve was ligated and the degenerative changes were studied by monthly biopsies over a period of ten months. In two other experiments, immediate anastomosis of the nerve was done as a control. In one of these, biopsies were taken at intervals of two weeks over a period of three months, at which time the nerve was examined by faradic stimulation and found to be functioning. Monthly biopsies were continued in this case for five additional months. Monthly biopsies, also, were obtained in the second control experiment. By using both sides of the animals, twelve successful experiments were obtained on seven dogs. One hundred and fifty-one biopsies were obtained in these twelve experiments and form the basis of this report.

PATHOLOGIC STUDIES

To avoid distortion, the biopsy specimens were stretched over wooden (tongue blade) blocks and held in place by sutures. The specimens were then fixed in a 10 per cent solution of formalin and, following fixation, each specimen was divided into two parts. Routine hematoxylin and eosin stains were used on one part and the other was reserved for the study of nerve endings and end-organs. Various stains were tried for nerve endings and end-organs and a modified Bodian stain was found to give the best and most consistent results. For the muscle used in this experiment better results were obtained by making frozen sections instead of mounting the specimens in paraffin and cutting as suggested by Bodian.[2]

The ten best-stained sections from each specimen were selected for study. The stains used proved of value not only in showing the nerve endings and end-organs but also gave an excellent picture of the changes occurring in the muscle fibers and compared favorably in this respect with routine hematoxylin and eosin stains. In fact the cross striations and vascular elements stood out more clearly with the Bodian stain than with the hematoxylin and eosin stains which were, therefore, used only as a check on the results observed with the colloidal silver.

RESULTS

Excellent descriptions of the various phases of degeneration and regeneration of nerve and muscle have been given in detail in other studies. It is not the purpose of this report to give a confirmatory review of these findings, and only those changes will be considered which bear upon the immediate problem, namely, the question of the relative capacity for regeneration of the various components of the neuro-muscular unit.

[2] Bodian, D.: New Method for Staining Nerve Fiber and Nerve Endings in Mounted Paraffin Sections. Anat. Rec., 65: 89–97, 1936.

Regardless of the interval of delay between the ligation of the thoracodorsalis nerve and its anastomosis, an abundant regeneration of the nerve never failed to occur in the eleven instances in which the dogs' thoracodorsalis nerves were anastomosed. No correlation could be established between the interval between ligation and anastomosis and the extent of the regeneration of the nerve or the formation of new nerve endings. The nerve endings and end-organs grew as abundantly after the nerve had been ligated for four months (the regeneration was observed five months after the original ligation of the nerve) as after one month or even after immediate anastomosis.

The alterations characteristic of the degeneration of muscle were seen to terminate in progressive fibrosis. Although surviving muscle cells were surprisingly rejuvenated following reinnervation in areas which were apparently hopelessly fibrosed, the functional recovery of the muscle appeared to be limited by two factors, first, the loss of muscle cells or potential contractile units and secondly, fibrosis. In spite of a considerable degree of successful reinnervation, fibrosis may mechanically impair the contractile activity of the residual and recovering muscle fibers. A study of the experimental material obtained in this study suggests that the degree of destruction of muscle cells and the extensiveness of fibrosis are in general comparable and that both are roughly proportional to the duration of the degenerative phase. Although time is probably not the only controlling element, it is apparently the principal factor which can be correlated in all instances with the extensiveness of these degenerative changes.

It should be observed that, following the anastomosis of the nerve in these experiments, the reinnervation and recovery of the muscle fibers are associated with apparent regression of the fibrotic process. This disappearance of fibrosis is presumably more apparent than real and results from a combination of the cicatrical contracture of the fibrotic process and its displacement by regenerating muscle fibers. This apparent regression of fibrosis was found to occur much more markedly in some areas than in others in the same muscle and, in general, was observed chiefly in those areas in which a relatively large number of muscle fibers and cells persisted. Correspondingly, this phenomenon was found to a greater extent in those experiments in which the duration of the degenerative phase was relatively short, that is, the muscles in these experiments made a more complete and perfect recovery. Thus, in the same fashion that the loss of muscle cells and fibrosis were found to be roughly proportional to each other and to the duration of degeneration, the disappearance of fibrosis may likewise be said in general to be inversely proportional to these same factors; that is, the greater the degree of fibrosis and loss of muscle fibers, the more fibrosis was observed in the regenerative phase of these experiments.

DISCUSSION

The possibility of correlating some characteristic pathologic picture with the failure of muscular recovery was anticipated in this study and, as previously noted, was found to be relatively dependent upon the degree of loss of muscle

fibers and cells and the extensiveness of the associated fibrosis of the muscle. In addition we hoped that these characteristic pathologic changes would prove of practical value in that biopsies on human muscle, obtained at varying periods following injuries to nerves, could be utilized to prognosticate the relative degree of recovery that might be expected, and thus determine the advisability of operative intervention in individual cases. This hope was not realized. A variety of pathologic changes was evident not only in material obtained from different parts of the same muscle, but also in different parts of the same biopsy specimen, demonstrating the impracticability of forming a valid judgment as to the prognosis and indication for operation in the individual case on the basis of the pathological study obtained by the limited technique ordinarily employed. Even though generous biopsies were obtained and numerous sections were prepared in this study, it was found that striking inconsistencies occurred in the serial biopsies of these experiments. Great variations in the stage of degeneration, apparently inconsistent with their relative chronologic position in the series, were frequently found in the serial biopsies taken from dogs. Although the sequence of pathologic changes observed in the serial biopsies as a whole gave a definite and unmistakable picture of the trend of the biological changes occurring in the various stages of degeneration, a false impression could readily be formed on the basis of a study limited to certain biopsies in the series. This was likewise true in the serial biopsies obtained during the regenerative phase of these experiments. Although of less practical significance, the variations from biopsy to biopsy were found to be more inconsistent during regeneration than degeneration.

The intervals between ligation and anastomosis of the nerve in these experiments may seem relatively short from the standpoint of degenerative and regenerative processes in the nerves and muscles of man, but the higher metabolism of tissue and greater power of regeneration in dogs make these intervals roughly equivalent to periods of twice these durations in man. Thus, degenerative periods corresponding in man roughly from two months to a year were obtained in this study, with subsequent anastomosis and follow-up of the regenerative process over periods which would correspond in man to an additional period of a year.

CONCLUSIONS

1. Ligation of the dog's thoracodorsalis nerve within its sheath, under the conditions described, affords a satisfactory method for obtaining uninterrupted degenerative changes in the latissimus dorsi muscle.

2. Serial biopsies of the latissimus dorsi muscles of dogs, obtained by this method over varying controlled periods of degeneration, showed a progressive loss of muscle cells and a terminal development of fibrosis, both of which roughly corresponded to the period of degeneration.

3. Serial biopsies of the same muscles in a regenerative phase instituted by anastomosis of the thoracodorsalis nerve, showed no appreciable variation in the abundance of regenerating nerve endings or end-organs following anastomosis

of nerves. This finding remained the same whether the anastomosis was performed immediately or after intervals of several months. The observation was interpreted as ruling out the nerve elements as a possible cause of the failure of muscular recovery.

4. Serial biopsies of muscle during regeneration showed a disappearance of the fibrotic process, most evident in the areas where relatively numerous muscle cells had survived and fibrosis was correspondingly more limited. Areas in which a high percentage of the muscle fibers and cells had been destroyed and in which extensive terminal fibrosis had occurred failed to show the same degree of improvement during the regenerative phase. These changes, namely the loss of potential contractile units and the mechanical fixation of fibrosis, were thus associated with the failure of muscular recovery.

5. The variation of pathologic changes to be found in different areas of the same muscle militates against the practicability of using single biopsies of human muscle as an index to the recovery of the muscle or the advisability of operation in any given case.

PROLONGED DEPRESSIVE PSYCHOSIS (TOXIC) DUE TO CHRONIC PULMONARY ABSCESS

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It is generally known that cerebral manifestations are rather common complications of pulmonary suppuration and that suppurative cerebral foci are by no means rare following surgical procedures for chronic suppurative pulmonary disease. Ira Cohen has called special attention to some of the features which characterize cerebral complications of putrid pleuro-pulmonary suppuration.[1] The following case cannot be grouped with any of the varieties of cerebral suppuration. It is presented as illustrative of the fine discernment in diagnosis and therapeutic judgment which characterized Dr. Sachs during his medical career.

CASE REPORT

M. F. came under Dr. Sachs' observation in 1927 because of a depressive psychosis of two years' duration. The additional history was that following a pneumonia in 1924, the patient began to expectorate quantities of non-fetid pus. At first there were prolonged episodes of fever, but subsequently fever occurred at irregular intervals and usually for short periods of time. There were several episodes in which there was high fever with thoracic pain, presumably due to additional pneumonic invasion. The onset of the psychosis appeared to coincide with one of these episodes. The psychotic state was characterized by disorientation and by depression which progressively became more profound. The patient had received sanatorium therapy during most of the period. Concerning the treatment of the pulmonary condition, therapy had consisted solely of postural drainage. Thus, at the time that the patient came under Dr. Sachs' observation the picture was one of a confirmed depression psychosis and an equally confirmed chronic pulmonary abscess. Those who had seen the patient before Dr. Sachs, appeared to believe that these were unrelated. Dr. Sachs first pointed out the possibility or even the probability of an interrelation. In his opinion, the only way in which the question of cause and effect could be settled would be by adequate care of the suppurative pulmonary lesion. Accordingly, the latter was studied from the viewpoint of some conservative surgical procedure which would or might care for the lesion since a radical procedure could not be considered because of the poor general condition of the patient. The abscess was localized to the upper lobe and the impression was gained that it had perforated anteriorly to make a pleural encapsulation in the subclavicular region. Operation was therefore decided upon with the view to establishing drainage of the empyema and of the communicating pulmonary abscess.

The patient was transferred from a sanatorium to The Mount Sinai Hospital for operation in December 1927. The general condition was one of profound apathy and advanced emaciation. Scarcely any local anesthesia was required for the operative procedure, the response to ordinarily painful stimuli being in abeyance. The operative procedure consisted in a subclavicular approach with excision of segments of the second and third ribs. A large chronic empyema was entered. The communication between this and the pulmonary cavity was enlarged, thus converting the pulmonary cavity and empyema into a single

[1] Cohen, I.: Cerebral complications of putrid pleuro-pulmonary suppuration. Arch. Neurol. & Psychiat., 32: 174–183, 1934.

space communicating with the anterior thoracic wound. The immediate postoperative course was characterized by prompt cessation in the expectoration of pus. There was profuse discharge from the wound which progressively diminished. Subsequently the wound reduced in size down to a narrow tract with bronchial fistulae at its bottom. A tube was kept in place for the maintenance of the bronchial fistula. Improvement of the psychotic state began a few weeks after operation and was exceedingly slow, but on the whole progressive. Six months after operation the general condition was excellent and the improvement was obvious. From that time on improvement was progressive. A year after operation complete recovery from the psychotic state could be recorded. When last seen in 1935, eight years after operation, the patient was entirely symptom-free.

POTENTIAL CHANGES IN INJURED AND UNINJURED MUSCLE DURING TETANUS PRODUCED BY STIMULATION BY INDUCED CURRENT[1]

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Although we have already reported in earlier studies upon "negative" and "positive variation" (1), we feel that it is necessary to repeat some of the conclusions reached and give the reasons for them, better to introduce the results of subsequent investigations here presented.

Between 1840 and 1843, the existence of a difference of potential between that of the uninjured, "natural longitudinal section" of a muscle and the cut surface or injured, "artificial cross section," was almost simultaneously described by Matteucci and E. du Bois-Reymond. When a circuit is closed connecting these points of different potentials a current flows in the external circuit from the uninjured or positive potential to the injured or negative potential and has been called variously the "muscle current" or the demarcation current.

Matteucci, without knowledge of a discovery made by du Bois-Reymond, had found as far back as 1838 that the above defined demarcation current was much weakened or completely disappeared during tetanus of the muscle. du Bois-Reymond, who had in the meantime formulated "the law of the muscle current," in 1842, showed that the demarcation current of a gastrocnemius diminished when its nerve was tetanized. This change in the output of the demarcation current he called "negative variation," the term originally meaning a diminution of the previously existing demarcation current without reference to polarity as understood in electrophysics. In his subsequent writings du Bois-Reymond, defined "negative variation" as the integral of the galvanometric effects of a rapid succession of excitation waves and of the effect of the diminished output of the demarcation current.

Sanderson (2) demonstrated (by means of a capillary electrometer) the integral of the electromotive changes postulated by du Bois-Reymond and said that the electrical phenomena of the negative variation in experimental tetanus of an injured muscle may be described as consisting of "1) a succession of excitation waves, each of which is evoked by an instantaneous stimulus and is expressed in the photograph curve by spike and hump, and 2), of a persistent state of excitation of the muscle, marked by diminution of the previously existing difference of potential between the sound and injured surface."

Clearly recognizing these two separate phenomena he wished to use the term negative variation for the diminished E. M. F., if it were not certain that it would be misunderstood. Feeling sure that its use would lead to confusion, he said, "I have recourse to the clumsy word 'diminutional' and call this persistent

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concomitant of continuous excitation of muscle, the 'diminutional' effect. For notwithstanding that du Bois-Reymond's original definition covers it, the phenomena are entirely different from those of tetanic 'negative variation' as described by du Bois-Reymond in his subsequent writing."

The study of our observations upon the electromotive accompaniments of continuous excitation of injured muscle deals with the persistent change which Sanderson called diminutional effect when the E. M. F. is diminished. Although we also fear that the term negative variation will at this time likewise be misunderstood, we elect to designate the persistent diminution of the E. M. F. of the demarcation current when an injured muscle is continuously excited the negative variation and when the E. M. F. is increased, the positive variation. There are two reasons for this: first, because du Bois-Reymond originally termed the diminutional effect or the lessening or disappearance of the demarcation current, the "negative variation" without any thought of an electrical sign. Second, although we agreed that the concomitant electrical phenomena of a change produced by continuous excitation of an injured muscle consists of both the succession of excitation waves and a persistent change in potential difference between injured and uninjured surfaces, we believe that with the recording apparatus available to du Bois-Reymond, galvanometers having a long period, an integral of the successive excitation waves, or an average value of their current could not have been recorded. In fact, he was able only to record the slow persistent change in the potential difference. We believe this to be true because of the following observations:

First, in a number of experiments, when D'Arsonval galvanometers with a period of 3 and 5 seconds respectively, comparing favorably to the galvanometers in use by du Bois-Reymond, were placed in series with non-polarizable electrodes upon a proximal uninjured part of a sartorius muscle and a distal injured part of the muscle, a deflection of the beam indicated by the demarcation current, a difference of potential. Now, when the muscle was stimulated directly by a faradic current, from an inductorium, of an average value of .15 volt, the demarcation current diminished until it almost disappeared. When a condenser with a capacity of 15 m. f. was placed in series in this circuit, as expected, there was no deflection of the beam since a continuous current could not pass through the condenser. But when the muscle was stimulated as above there likewise was no movement of the beam. Since transient currents do pass through a condenser, it was obvious that this particular galvanometer was incapable of recording them.

Second, it was found that when a sartorius muscle was directly stimulated by a faradic current, through bi-polar platinum electrodes, the direction of the transient waves accompanying each stimulus, and probably related to escape or "shock effect," could be changed by changing the direction of the stimulating current and recorded by an Einthoven galvanometer, deflections originally "south" becoming "north." When in each experiment, the changes were also observed in a D'Arsonval galvonometer it was found that the change in the demarcation current, for example, a diminution, in the case where the distal end

of the muscle was injured, was unaffected by the change of polarity of the stimulating current producing transients which were of the order of those observed by Sanderson. This we took to mean that the integral of the transients or the average value of their current was not followed by the D'Arsonval galvanometer and that only the slow persistent change was recorded.

Furthermore, if one studies the illustrations of the galvanometric curves of Waller's (3) contribution, it will be found that irrespective of whether north or south deflections followed single stimuli before continued stimulation by a tetanizing current or whether after such stimulation or treatment of a nerve by carbon dioxide the deflections changed from south to north or vice versa, that during the period of continuous stimulation by a tetanizing current there was a diminution of the demarcation current in practically all.

Third, the order of the potential difference in the case of negative variation is often 32 millivolts whereas an average action potential of a bull frog's peroneal nerve is only about 2 millivolts.

In our study of slow persistent change, as we had expected, when we examined the effect of indirect and direct faradic stimulation of a muscle upon the demarcation current produced by injuring the distal end of the muscle, we confirmed the earlier observations of a resultant diminution of the demarcation current, i. e., of a resultant negative variation.

Although many more experiments were performed than we have recorded, records of thirty-three preparations show that the potential differences existing between the surface of the muscle and its injured end ranged from 2.01×10^{-3} volt to 13.24×10^{-3} volt; the demarcation currents ranged from 1.6×10^{-9} ampere to 8.4×10^{-9} ampere. In thirty of thirty-three preparations (gastrocnemius and sartorius) the change was as expected, a diminution, i. e., a negative variation. Upon stimulation of the muscle specimen, the value of the demarcation current was diminished from 17 to 100 per cent of its original value; occasionally, the polarity of the demarcation was reversed. That is the diminution of the demarcation current was so marked that the direction of current flow was reversed.

In the foregoing experiments, the non-injured portion of the muscle lies between the stimulating electrodes and the injured area of the muscle. Any explanation of the du Bois-Reymond effect, or "negative variation" or the diminution of the demarcation current when a muscle or nerve is stimulated, should be applicable to any change that occurs when the polarity of the demarcation current is reversed.

In order to reverse the polarity of the demarcation current the injury was placed in the proximal part of the muscle. This produced an injury of the muscle so that a demarcation current resulted, the direction of which showed that at least the surface of the proximal portion of the muscle was "negative" in regard to the ends of the muscle, though conduction still occurred through the injured portion. When direct stimulation of muscle was desired about 2 mm. of sartorius muscle was left uninjured at the extreme proximal part.

In 25 out of 29 preparations, when the muscle was stimulated directly proximal

to the injured portion, the original demarcation current showed an augmentation rather than a diminution.

In these experiments the original demarcation current ranged from 1.6×10^{-9} to 8.4×10^{-9} ampere. The augmentation of the current on stimulation ranged from 16 to 200 per cent of the original.

In 14 of 16 preparations the muscle was stimulated indirectly through its nerve. The demarcation current was augmented by from 10 to 100 per cent of the original value.

In 6 experiments using the sciatic nerve in which the injury and electrodes were placed as in the experiments on muscle, an augmentation of the demarcation current of from 20 to 200 per cent occurred.

The augmentation of the demarcation current occurred without regard to the polarity of the stimulating current. Thus, it is clear that when the demarcation current is reversed, so that the injured area of lower potential is located between the stimulating electrodes and the distal lead of the galvanometer, an augmentation of the demarcation current occurs instead of a diminution.

The polarity of the excitatory waves or action current namely an excitation wave or wave of negativity passing first under the proximal and then under the distal lead-off can not explain the slow persistent change originally called negative variation by du Bois-Reymond and a diminutional effect by Sanderson. Not only is the direction of the excitatory waves unrelated to the direction of the slow persistent change but obviously, when under the proximal lead-off there is a negative injury potential, and a condition of electronegativity is produced in the uninjured active portion of the muscle under the distal lead-off, when an excitation wave or wave of negativity passes over it, a diminution of potential difference should occur and a diminution of the demarcation current result. The opposite effect is usually observed. Whenever the proximal lead-off is over a negative injury potential the demarcation current is increased when the muscle is stimulated by a tetanizing current. When the distal lead-off is over a negative injury potential a diminution of the demarcation current results. In both instances the change in the potential difference is to make the proximal end relatively negative, the distal relatively more positive irrespective of which end is injured.

In an effort to discover the cause of this electrochemical change we have, following the original report, attempted to determine whether the change in potential occurred only at the uninjured portion of the muscle or at the injured part as well. To determine this the relative potential of the injured and uninjured portion of the muscles was measured by two methods of using exploring and indifferent electrodes in volume conductors.

The distribution of electric currents in volume conductors has been studied by Craib (4), Wilson (5), Wilson, Macleod and Barker (6), Eyster, Maresh and Krasno (7) and others and more recently by Sugi (8) both in heart and skeletal muscle. In addition to mapping out the fields, studies have also been made by them upon the form of action potentials in various parts of the field.

In one method, the exploring electrode was placed upon the heart and the

other, indifferent or distal electrode at some distance from the heart, usually the left hand leg. We have used a similar method by placing the exploring electrode upon the part of the gastrocnemius muscle whose potential changes were being studied and the other indifferent, electrode upon the opposite gastrocnemius muscle.

In other studies, the tissue to be studied was immersed wholly or partly in saline or Ringer's solution, the exploring electrode was placed upon the tissue to be studied and the indifferent electrode into the saline or Ringer's solution. This method recently carefully described by Sugi was also used by us.

The theory underlying these experiments is based upon the assumption that, in a large conducting medium surrounding a source of potential, when the exploring electrode is placed directly upon the tissue to be examined and the indifferent electrode at a distance in the conducting medium or bath, the changes in potential at the indifferent electrode are so small that they may be disregarded and this electrode may be used as a reference point to which changes under the exploring electrode may be compared.

Although this view has been attacked by Bishop and Gilson (9), we believe that for our purpose which is qualitative rather than quantitative, the method is sound to determine the direction of change in potential at investigated ends of muscle and to compare the relative degree of changes observed.

METHOD

In both experiments, using different types of volume conductors the stimulating electrodes consisted of two platinum points in an insulated holder. The nerve was stimulated by a series of induced currents for which purpose a Harvard inductorium was used.

The lead-off electrodes were of silver-silver chloride type. The electrode was immersed in normal sodium chloride solution, the muscle connected with two liquid junctions by means of braided silk soaked in normal sodium chloride solution. The potential difference was measured by an ultra sensitive vacuum tube direct current meter with a resistance of the volmeter circuit of 5 megohms.[2]

Experiment 1. The lower part of the spinal cord of a frog having been removed, the sciatic nerve on one side was dissected free, severed, and the distal end used for stimulation purposes. The sciatic nerve of the opposite side was severed.

The whole frog, with the skin removed over both gastrocnemii, was placed upon an ebonite board which was covered by filter paper moistened with Ringer's solution. The legs were immobilized, so that very little shortening of the gastrocnemius muscle occurred upon stimulation.

The exploring electrode was placed upon the part of the muscle whose potential changes it was desired to study. The indifferent electrode was placed upon the opposite gastrocnemius muscle. When the exploring electrode rested upon an area with a negative potential as the distal end of an uninjured muscle or the

[2] Ultra sensitive D. C. Meter #9819 R. C. A. Manufacturing Co.

proximal injured part of the muscle, the indifferent electrode was placed upon a positive portion of the opposite gastrocnemius muscle.

To confirm the belief that little change in potential occurred under the indifferent electrode in the unstimulated opposite gastrocnemius muscle, measurements were made of the P. D. between the proximal and distal ends of the muscle when the opposite one was stimulated and no change was found. Furthermore when under similar conditions a salt bridge was placed from the proximal or distal ends of the unstimulated muscle to the opposite end of the stimulated one, producing the same current pathway as would be present when the exploring electrode was on the stimulated muscle and the indifferent electrode on the unstimulated one, no change in P. D. appeared. We concluded that such change as may occur at the indifferent electrode was negligible and the method suitable for our purpose.

The muscle was injured either by immersing the distal end into water at 160° F. or when it was desired to injure the proximal end, by applying a Bovie knife until a coagulation bleb appeared.

Experiment 2. The circuit employed was similar to that illustrated by Sugi (loc. cit.) (fig. 1).

A frog prepared as in experiment 1, tied to an ebonite board covered with filter paper, was immersed in a large petri dish filled with Ringer's solution, partly submerging the gastrocnemius muscle to be studied. Two other petri dishes filled with Ringer's solution were connected to the bath by strands of silk moistened with Ringer's solution. The exploring electrode was placed upon the desired part of the muscle to be stimulated and the indifferent electrode in one of the other petri dishes.

Results. Experiment 1. (A). Uninjured muscle. In the uninjured gastrocnemius muscle, when the exploring electrode was on the proximal end of the muscle to be stimulated and the indifferent one on the distal end of the opposite gastrocnemius muscle, and the exploring electrode was positive to the indifferent electrode of from 8 to 32 millivolts, tetanus produced by stimulating the sciatic nerve by faradic current, resulted in a potential change of diminished positivity of from 2 to 19 millivolts.

When in the uninjured gastrocnemius muscle the exploring electrode was upon the distal end and the potential negative to the reference electrode from 16 to 38 millivolts, upon stimulation there was a decrease of negativity of from 2 to 21 millivolts.

It is seen that in the uninjured muscle indirect stimulation of the muscle by faradic current resulted in a diminution of positivity or a greater negativity at the proximal end, and a diminution of negativity or greater positivity at the distal end.

(B) The proximal end of the gastrocnemius muscle is injured.

When the proximal end of the gastrocnemius muscle was injured and the exploring electrode was on the injured proximal part of the muscle, and was negative to the indifferent electrode on the opposite gastrocnemius muscle, by from 4 to 36 millivolts, when the muscle is stimulated, there is a change of potential

making the exploring electrode more negative by from 2 to 8 millivolts. When under the same condition the exploring electrode is on the distal uninjured part of the same muscle and is negative to the indifferent electrode or the proximal end of the opposite gastrocnemius muscle by from 14 to 26 millivolts, on stimulation there is a potential change making the exploring electrode more positive by from 4 to 20 millivolts.

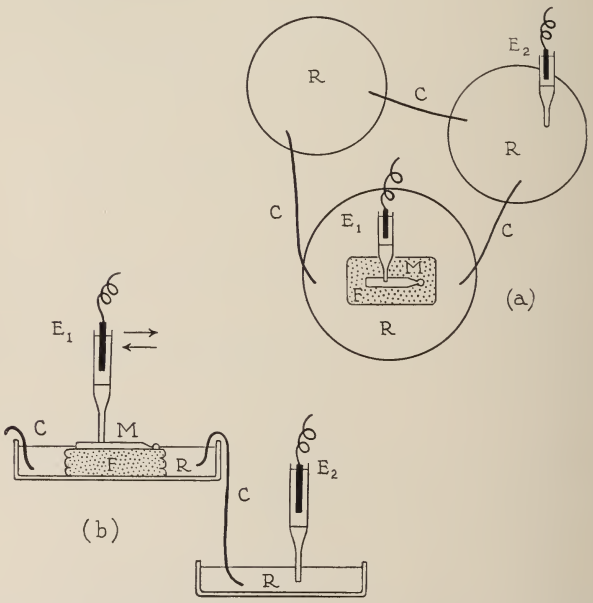

FIG. 1. Schematic illustration of the apparatus (adapted after Y. Sugi). a, top view; b, side view; M, muscle; E_1, exploring electrode; C, strands of wet silk thread; F, bakelite holder covered with filter paper; E_2, indifferent electrode; R, Ringer's solution.

It is seen that when the proximal end of a gastrocnemius muscle is injured indirect stimulation of the muscle produces an increase of negativity at the proximal end of the muscle and of positivity at the distal end.

(C) The distal end of the gastrocnemius muscle is injured.

When the distal end of the gastrocnemius muscle was injured and the exploring electrode was on the proximal part of the muscle and was positive to the reference electrode on the distal end of the opposite gastrocnemius muscle by from 10 to 20 millivolts, upon stimulation there was increase of negativity of 2

to 4 millivolts. When the exploring electrode was on the injured distal part of the muscle and negative to the indifferent electrode by from 21 to 56 millivolts, on stimulation there was an increase of positivity of from 12 to 38 millivolts.

Thus, when the distal end of a gastrocnemius muscle is injured and it is indirectly stimulated by a faradic current, the proximal end becomes only very slightly more negative and the distal end markedly more positive.

DISCUSSION

Combining all these preparations it is seen that when a gastrocnemius muscle is indirectly stimulated by a faradic current applied to the sciatic nerve, the proximal end of the muscle becomes more negative and the distal end more positive, whether the muscle is uninjured, injured at the proximal part or injured at the distal part. However, when either the distal or proximal part of the muscle is injured, the change of potential at the proximal part is disproportionately small as compared with the change at the distal part of the muscle.

Experiment 2. As already explained, in this experiment, the exploring electrode is placed upon the desired part of a gastrocnemius muscle which is to be stimulated, the frog being immersed in a bath of Ringer's solution, partly submerging the muscle. The indifferent electrode is placed in one of the other dishes containing Ringer's solution and which are connected to the bath by strands of silk moistened with Ringer's solution.

In this experiment we obtained potentials from proximal and distal ends of the muscle both when proximal and when distal ends were injured and from proximal middle parts and distal ends of the muscle, when the middle of the muscle was injured.

When the proximal end was injured and the muscle stimulated there was an increase of negativity at the proximal end of from 1 to 6 millivolts. When the distal end was injured and the muscle stimulated there was a decrease of positivity or increase of negativity at the proximal end of from 4 to 6 millivolts, and a decrease of negativity or an increase of positivity at the distal end of from 4 to 20 millivolts.

When the middle portion of the muscle was injured, there was a decrease of positivity at the proximal uninjured end of from 4 to 5 millivolts, an increase of negativity at the middle injured portion of from 4 to 10 millivolts and at the distal uninjured portion a decrease of negativity or increase of positivity of from 3.5 to 6 millivolts.

In these experiments which consist of determining the change in the electric field at certain points, when distal or proximal ends were injured as in our other experiments, the proximal end of the muscle became more negative and the distal end more positive, when the muscle was tetanized. But when the middle portion of the muscle was injured, it as well as the uninjured part of the muscle became more positive. Thus, when the muscle was injured proximally, the injured part became more negative and when it was injured at the middle, the injured part became more positive when stimulated. It follows that it is not only the change produced by the injury, and at the electrode which is responsible

for the change in the potential but a change at some distance from that region. There is an increase of negativity proximal to the junction between uninjured and injured muscle and an increase in positivity distal to the junction.

The results of both of our experiments confirm the conclusion reached from our former study and clearly indicate that the ordinarily accepted explanation for negative variation in the sense of du Bois-Reymond (negativity of uninjured active part of the muscle) is incorrect. Not only does the uninjured distal part of the muscle not become negative but on the other hand becomes strongly more positive.

We are unable to state what causes the change in potential at various points of the muscle. However, it is suggestive of a rearrangement of dipoles, the orientation of which had been established by points of injury.

CONCLUSIONS

1. When stimulated, the gastrocnemius muscle becomes more negative at the proximal and more positive at the distal end whether it is uninjured, injured at the proximal or at the distal end.

2. When injured at the middle, the gastrocnemius muscle when stimulated, becomes more negative at the proximal uninjured part, more positive at the middle injured part and at the uninjured distal part.

3. The part of the muscle proximal to the junction between uninjured and injured muscle becomes more negative when the muscle is stimulated, that distal to the junction more positive whether this part is injured or not.

4. Neither the theory explaining the polarity of the monophasic excitatory wave (wave of negativity) nor that assuming that when stimulated, the uninjured active part of the muscle becomes relatively electro-negative, explains the direction of the slow, persistent change of the preexisting demarcation current which du Bois-Reymond designated "negative variation."

5. Although we do not know the cause of this orientation of change in potentials, it is suggested that it is concerned with a rearrangement of dipoles from that produced by an injury upon a muscle in its resting state.

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THE REPRESENTATION OF THE CENTRAL FOVEAE AND OF THE HORIZONTAL MERIDIANS IN THE VISUAL RADIATION (RADIATIO OPTICA) OF THE HUMAN BRAIN[1]

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It is common knowledge that since the opening of the era of modern brain investigation seventy years ago the visual system has been an object of continuous interest. Especially numerous are the studies dealing with the problem of the representation of the retina in the brain. The result of these efforts is a fairly detailed knowledge of the location of various quadrants of the extra-foveal periphery, and of the fovea (the so-called "macula") in the lateral geniculate nucleus and in the visual cortex, the striate area of the occipital lobe. Less certain is the arrangement of the quadrants, the location of the foveal fibers—the so-called "macular bundle"—and the representation of the horizontal meridians, in the visual radiation.

In the following, is the report of a case, which, in a very clear way shows the position of both the horizontal meridians and of the foveal ("macular") fibers in the radiation.

CASE REPORT

History: The patient, Le Roy M., 22 years old, had suffered since childhood from "rheumatism" and an indefinite heart trouble. The present illness began fifty-eight days before death with a sudden headache in the right fronto-parietal region, associated with "double vision in the right eye and blindness in the temporal half of the left eye." Fifteen minutes after the onset the patient felt nauseated and vomited. The tentative diagnosis made was that of a subacute bacterial endocarditis with bacteremia. This was confirmed by the cultures made from blood which showed the presence of streptococcus viridans.

Ophthalmological examination: A left incomplete inferior quadrantic homonymous hemianopia (fig. 1, upper fields) was revealed. The visual fields were plotted for the first time thirteen days after the onset, which was forty-five days before death. The blindness extended also into the upper half of the monocular crescentic field of the left eye. The central portions of the affected quadrants were spared as far as three or four degrees from the fixation points. In addition, there was a cotton-wool exudate in the right retina at the first branching of the superior temporal vein about 1.5 x 3 times the diameter of the vein. The second plotting was made eleven days after the first, or thirty-four days before death (fig. 1, lower fields). This time the upper left crescentic field was found almost restored and the blindness practically limited to the left inferior homonymous quadrants. As before, the central vision was spared. This situation remained substantially the same until death. The target for plotting was 3 mm., white, used at 33 cm. distance, by daylight. On both occasions the patient was ill due to the high fever which persisted until the last, but was as cooperative as he could possibly be.

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[2] For the clinical data and for the brain specimen this writer is indebted to Dr. F. Burch, Minnesota University Medical School, St. Paul, Minnesota, and Dr. C. W. Rucker, Mayo Clinic, Rochester, Minnesota.

Necropsy findings: The pathological anatomical examination corroborated and amplified the clinical diagnosis by the presence of a chronic endocarditis. Infarcts were found in the spleen, kidneys and brain. The brain had a cyst in the right occipital lobe, but appeared otherwise normal. There were no signs of meningitis.

The *right occipital lobe*, grossly examined, showed on the lateral face, near the dorsal margin, a small focus of softening the extent of which could not be determined beforehand. Serial sections stained with the methods of Weigert-Kulchitsky, Van Gieson and hema-

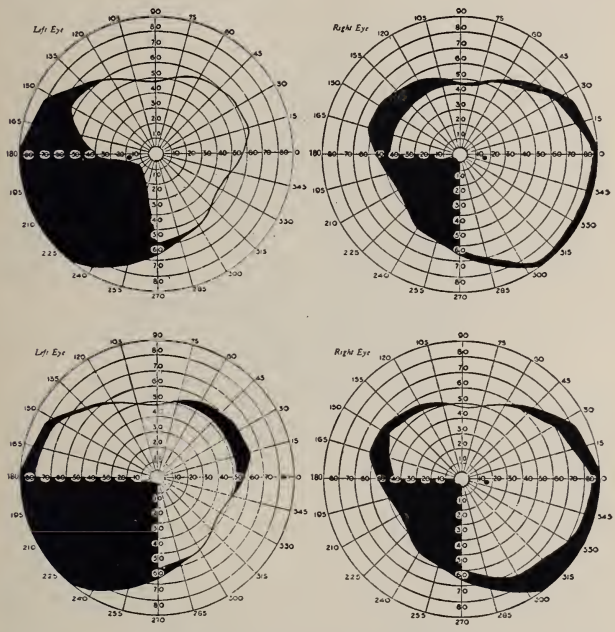

Fig. 1. Visual field defects of the homonymous quadrantic type due to an uncomplicated unilateral partial lesion of the opposite visual radiation. Upper fields 47 days, lower fields 34 days before death.

toxylin-eosin revealed the presence of a single cystically degenerated crescent-shaped, vertically placed cavity (fig. 2, *les*). This focus extended on the one hand from the surface of the brain through the white subcortical mass down to the ependyma of the posterior horn of the lateral ventricle (*lv*), and, on the other hand, through almost the entire longitudinal extent of the lobe. The cavity was lined by a reactive membrane which was everywhere even and smooth, without diffuse zones of transition or inflammatory infiltration. Obviously, the cavity was due to the resorption of the necrotic mass of the infarct caused by the clogging of a branch of the middle cerebral artery. The ultimate etiology of the lesion was the chronic endocarditis which produced the embolus.

A number of the cerebral structures were affected directly or indirectly by the lesion. The lower or ventral end of the cyst interrupted completely a solid portion of the sagittal fiber layers. Of the outer sagittal layer (*vis. rad.*, visual radiation, in fig. 3), on the anterior levels through the lobe, the upper or dorsal horizontal limb was found missing, with the exception of the innermost portion in the upper lip of the calcarine fissure. The adjoining portion of the vertical limb of the radiation was also interrupted. On levels closer to the tip of the occipital lobe (fig. 4) the lesion destroyed almost the entire upper or dorsal half

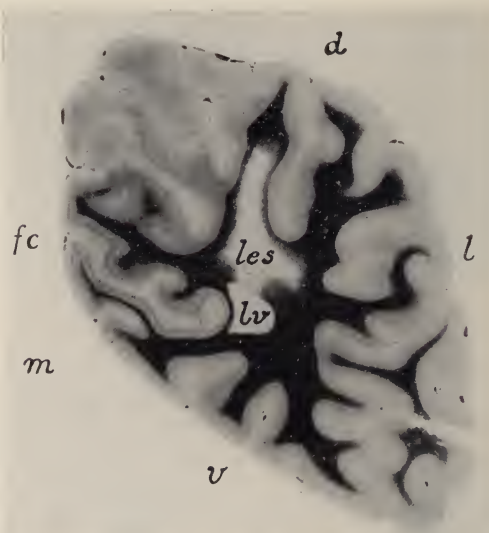

Fig. 2. Section through the right occipital lobe stained with Weigert's method, showing the single lesion (*les*) which interrupted the dorsal portion of the visual radiation, causing the contralateral homonymous quadrantic hemianopia. Dorsal face (*d*); calcarine fissure recognizable by the intracortical stripe of Gennari or Vic-d'Azyr (*fc*); lateral face (*l*); lesion (*les*); lateral ventricle (*lv*); medial face (*m*); ventral face of the hemisphere (*v*).

of the radiation, just sparing the lateral salient (marked with a cross) where the upper and lower limbs of the radiation join.

In the *right striate cortex* which lines the calcarine fissure the comportment of the fibers was as follows: In the anterior one-third of the longitudinal extent of the fissure the intracortical afferent visual fibers, distinguished by their slanting course, appeared normal in both lips (cf. fig. 65 (4a)). The subcortical fibers that line the "calcar avis" bulging in the lateral ventricle were likewise normal in this locality. In the middle one-third of the calcarine fissure, in its upper lip, the subcortical fibers, beginning with the deepest point of the fissure, were found considerably depleted. In the same locality the intracortical afferent visual fibers also were almost entirely absent. In the occipital or posterior one-third of the calcarine fissure, and in the tip of the lobe, the subcortical and the intracortical afferent visual fibers in the entire striate area appeared again normal.

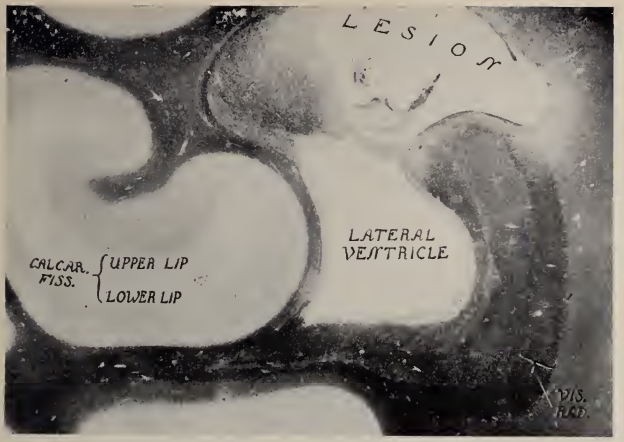

FIG. 3. Portion of fig. 2 at a higher magnification showing the structures surrounding the lateral ventricle. Note the three fiber layers which compose the so-called "sagittal layers of the occipital lobe," the most outward being the visual radiation. Note also the sharp delimitation of the lesion from the normal structures.

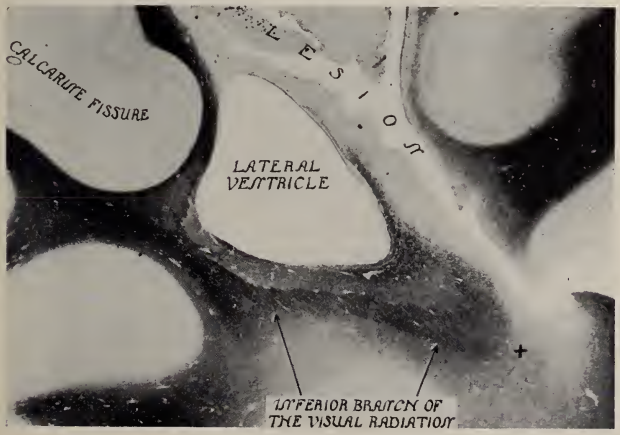

FIG. 4. Section closer to the tip of the occipital lobe than the one represented in figs. 2 and 3. Note the location and the extent of the lesion which interrupted the dorsal portion of the visual radiation, leaving the ventral portion and the lateral salient of the radiation (marked with a cross) intact or almost so.

In the *right lateral geniculate nucleus* (fig. 5), stained according to Nissl with the toluidine blue, a well-defined zone was found, where the nerve cells showed Nissl's "primary irritation" and "retrograde degeneration" in various stages, mostly far advanced, including complete disappearance. The zone resembled somewhat the shape of a wedge, with its broad end along the upper extremity, and its sharp point at the hilum of the nucleus. The position of the wedge, where it attained its greatest extent, was in the inner or medial segment of the nucleus (closer to the thalamus). Precisely, if the nucleus be divided on a cross section in the coronal plane into four segments, the second segment beginning from the medial tip degenerated completely. In the first, or the innermost segment, coinciding with the inner tip of the nucleus (*left*, in fig. 5), a number of the nerve cells appeared less affected. The degeneration passed through all six cellular layers including the ventral ones composed of large elements. In the outward or lateral one-half of the nucleus (*right*, in fig. 5) the

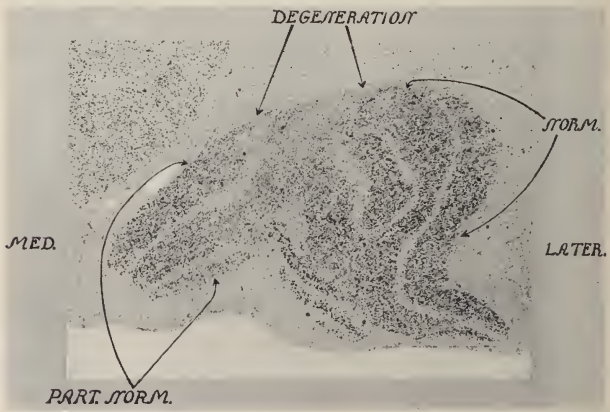

FIG. 5. Lateral geniculate nucleus of the same hemisphere stained with the toluidine blue according to Nissl-Lenhossék. Note the extent of the zone of retrograde degeneration and its location in the inner half of the nucleus (where only the tip contains fairly preserved nerve cells), while the outer or lateral half of the nucleus remained normal.

nerve cells appeared normal, compactly filling the cellular layers, except in the immediate vicinity of the degenerated zone. The degeneration was most complete in the center of the affected territory, where almost all cells were altered to a point as to be unrecognizable. The neuroglia, as usual in such retrograde foci, was greatly increased in numbers in the entire degenerated territory, when compared with the parts of the nucleus that remained normal. The position of the degenerated wedge, and likewise its shape, although in the main limited to the medial half of the nucleus, changed somewhat along its longitudinal extent. In the anterior or oral half of the nucleus the wedge extended to the midline, or even somewhat beyond it (this slanting line divides the nucleus into a smaller ventrolateral, and a larger dorsomedial portion). Midway of the longitudinal extent of the nucleus the degeneration occupied almost exactly the inner one-half of the nucleus (fig. 5). In the posterior or caudal third of the nucleus the affected zone was gradually reduced, until in the posterior tip (belonging exclusively to the fovea or "macula") it disappeared completely. Here, in approximately the posterior one-sixth—where the nucleus is composed

of only four cell layers, the two dorsal layers made up of small cells, and the two ventral layers accommodating larger cells—almost all cells preserved normal appearance. An exception was a few scattered nerve cells which were discolored or shrunk, probably a consequence of general factors (toxic agents, fever).

In addition to the large retrograde degeneration just described, caused by the distant interruption of a compact portion of the visual radiation, a few minute disseminated primary foci of infection, represented by the agglomeration of non-nervous cells, were found both in and outside the degenerated zone. These few fresh inflammatory nests, similar to those found here and there in other parts of the brain, were due to a recent slight disseminated encephalitic process, which in turn was caused by the cardiogenic bacteremia. Such foci could easily be dissociated from the large and solid retrograde degeneration, the more so, since the nerve cells located in the immediate vicinity of, or even imbedded into these tiny foci of inflammation, showed only slight degenerative changes, or none at all.

The *left lateral geniculate nucleus* was found to be normal. No clearly defined zones of degeneration, which could in any way be brought into connection with the partially interrupted visual radiation in the right occipital lobe, were found in it.

Patho-physiological Interpretation

The analysis of this case, unique because of a remarkably clear pathological anatomical situation, deserves special attention. In this respect the case is equal to the best experiment, with the additional advantage obtained from clinical observation.

First, the cortical lesion, because of its location far outside the striate area or the cortical visual center (in fig. 2 recognizable by the intracortical stripe of Gennari and Vicq-d'Azyr), must be ruled out as the possible cause of the homonymous quadrantic visual field defect. The striate cortex itself also was nowhere damaged. The functional loss must, therefore, be attributed entirely to the lesion of the subcortical fiber substance. Here again the destruction of the fibers outside the sagittal layers—which alone are concerned with the elemental visual functions—was irrelevant. Thus, by exclusion, the cause of the visual disturbance appears to be the partial interruption of the external sagittal layer which, as found by the previous pathological and experimental investigations (cf. 4a), contains the afferent fibers of the visual radiation.

The next fact of consequence is the almost complete interruption of the upper horizontal limb or branch of the radiation in the anterior levels through the occipital lobe (figs. 2, 3). This branch terminates in the upper calcarine lip, as clearly evidenced by the experiments with monkeys (cf. 4b). This well agrees with the functional defect which was limited to the opposite inferior homonymous quadrants of the visual fields (fig. 1, lower fields). The single lesion in this case had, accordingly, interrupted the fibers that carry impulses from the large peripheral or extrafoveal portions of the right upper homonymous halves of both retinae. This is evidenced, first, by the clinically observed functional defect—the left incomplete inferior quadrantic hemianopia, contralateral to the side of the lesion. In the first plotting, besides this, there was also a superior crescentic blindness on the left side (fig. 1, upper fields). This was likely due to a compression or some other interference with the normal blood supply (e.g., collateral edema) of the lower lip in the anterior extremity of the calcarine fissure

by the same focus which directly destroyed the upper segment of the visual radiation. The upper crescentic blindness, as was made fairly certain by the second plotting, was merely an initial symptom, disappearing afterwards and leaving as a permanent residue a simple incomplete blindness in the left inferior quadrants. The second evidence is the position of the degenerated zone in approximately the inner one-half of the lateral geniculate nucleus, the same where according to the experimental evidence the optic nerve fibers from the extra-foveal portions of the upper homonymous retinal quadrants terminate. The final evidence is the absence of the afferent nerve fibers in the striate cortex in the upper calcarine lip, in the middle one-third of this fissure, a locality related to the upper retinal, or the lower opposite field quadrants (as found by other means).

All this decidedly points toward the vertical division of the visual radiation, with the upper and lower extra-foveal or "peripheral" retinal quadrants represented in the upper and lower segments, and the homonymous halves of the foveae ("maculae") and of the central area of the two retinae represented in the intermediate or axial segment of the radiation placed between the first two. Such possibility was suggested already by Holmes (2) and advocated by Rönne (6). The same concept found further support in the observations by Putnam (5) and by Juba (3), and was experimentally demonstrated to be present in monkey by Heuven (1) and by this writer.

From the evidence of this case it is further certain that the assumption of the location of the "macular bundle" either in the dorsal portion (Pfeifer, Niessl von Mayendorf, et al.), or in the ventral portion of the visual radiation (Niessl von Mayendorf, et al.), or that the "macular fibers" may be scattered all over the visual radiation (Monakow), is incorrect. For, in spite of the almost complete destruction of the dorsal one-half of the radiation, the central portions of the affected quadrants were spared to the extent of from three to four degrees around the points of fixation. It is, therefore, apparent that the fibers which correspond to the preserved central portions of these quadrants must have been in the portions of the visual radiation that escaped destruction, and in the immediate vicinity of the lesion. Since these fibers originate in the intermediate foveal or "macular" segment of the lateral geniculate nucleus, which separates the lateral extra-foveal or extra-macular segment of the nucleus from the mesial (which intermediate segment was found to be normal here), and since the inferior limb of the radiation, which in this case remained intact, terminates in the inferior calcarine lip (where the inferior extra-foveal retinal quadrants are represented), the chain of the evidence seems to be complete in favor of the intermediate location of the foveal or "macular bundle" in the visual radiation—precisely the portion which also remained here largely intact (in fig. 4 marked with a cross).

In sections through the anterior part of the occipital lobe, the visual radiation resembles somewhat in shape a horseshoe, with an upper and a lower horizontal limb or branch, and with a vertical limb linking together the first two (figs. 2 and 3). The upper horizontal limb, destroyed here, is continuous with the vertical limb of the radiation. Accordingly, it is this vertical portion of the

radiation which, if one looks upon the radiation as a fan composed of rather parallel bundles of fibers, forms its "axial" or "central" segment. Here are located the fibers that represent both homonymous halves of the central area of the two retinae, including the foveae ("maculae"), up to three or four degrees on both sides of the horizontal meridians. On the levels closer to the tip of the occipital lobe the fiber layer of the visual radiation changes somewhat its shape. The vertical branch is transformed into an obtuse angle, with its point turned outward, and its concavity facing the calcarine fissure (fig. 4). Here it is more proper to speak of only an upper and a lower horizontal branch, and of a "lateral angle" or "lateral salient" of the visual radiation linking the two. The fibers of this salient in the present case just escaped injury. Further back, in the tip of the lobe, these fibers slip behind the posterior horn of the lateral ventricle and turn inward and backward in order to reach the most posterior portion of the striate cortex at the tip of the occipital lobe (found normal in present case). The most "central" or "axial segment" of the visual radiation, accordingly, remained in this case intact all the way from its origin in the caudal tip of the lateral geniculate nucleus of the same side to its terminal station in the tip of the occipital lobe. This anatomical observation is in accord with the fact of the sparing, and in turn explains the same sparing, of the central portions of the affected quadrants of the visual fields.

The reported case also illustrates the position of the horizontal meridians in the visual radiation. It shows that if the upper horizontal limb of the radiation is interrupted, the blind homonymous quadrants are separated from the seeing ones of the same sides by the straight horizontal lines which are the horizontal meridians. An exception is the small areas, corresponding with the central portions of the respective quadrants around the fixation points which may remain normal when the foveal or "macular" fibers are spared, as it apparently happened in this case. The only possible explanation of this remarkable feature—the linear delimitation of the quadrantic hemianopia—is the assumption of a sizable "anatomical interval" or a "gap" between those fibers of the radiation that represent the extra-foveal periphery of the upper, from the fibers that represent the same territory of the lower homonymous quadrants, as was suggested long ago by Gordon Holmes (2) and by Rönne (6) on the basis of the analysis of the clinical cases. There is no other mechanism, cortical or subcortical, which in cases of a partial destruction of the visual pathway would account for the strictly quadrantic hemianopic defects. The "gap" just mentioned, however, is not void, but is filled with the foveal or "macular" fibers. The foveal or "macular" fibers form, accordingly, the central or axial rib of the fiber fan that is the visual radiation (cf. fig. 100, (4b)). This foveal segment of the radiation, interposed as it is between the upper and the lower extra-foveal segments, serves as a "barrier" or "buffer." It prevents, because of its large size, many a limited lesion destroying one of the extra-foveal limbs from spreading to the other extra-foveal limb of the radiation. Only when an expanding lesion has passed that barrier, the other upper or the lower extra-foveal limb of the radiation, as the case may be, may be involved in the process. The necessary consequence of this peculiar

anatomical arrangement is that a homonymous quadrantic blindness, if it expands upon the adjoining quadrants of the same side, may not do so before it had eliminated, first, its own foveal or "macular" quadrants, and then the foveal portions of the invaded quadrants. Only after this the blindness may further spread over the extra-foveal portions and thus produce a complete hemianopia. In any case, the expanding amaurotic defects will creep along the horizontal meridians, in the first phase toward the fixation points until the completion of the quadrantic hemianopia, and in the invaded quadrants away from the fixation points.

In accepting this arrangement one has further to assume that—beginning with the most peripheral bundles at the upper and lower margins of the radiation closest to the upper and to the lower calcarine lip—each narrow subsequent segment of the outer sagittal fiber layer closer to the axial bundle represents a narrow concentric quadricircular belt or zone of the corresponding homonymous quadrants. These belts are necessarily the longest in the extreme field periphery, becoming gradually shorter the closer they lie to the points of fixation. Each of the fiber segments, in turn, is to be imagined as composed of a row or a series of minute bundles of (mostly) homonymous fibers, representing individual functional visual units, each capable of independent acting. Such series of the respective functional units make up each of the quadricircular belts in the corresponding homonymous visual quadrants. In the farther periphery of the fields the functional units are relatively large and few, and therefore a few fibers, that is, few neurons, in the visual radiation represent a relatively large territory. Closer to the fixation points the units gradually decrease in size and increase in numbers. This requires an increasing number of fibers, as the fixation points are approached.

Finally, the corollary of this conception requires that in purely subcortical lesions, caused by a single focus which interrupts a smaller or larger portion of the visual radiation, the field defect should always comprise a belt-shaped quadricircular zone. This blind zone will be either narrow, if a small segment of the radiation is damaged, or wide, if a broad segment is interrupted. The blindness may eventually spread over the entire upper or lower homonymous quadrants, if exactly one-half of the radiation is interrupted. A sparing of the fovea ("macula") in such cases is present or absent depending on whether or not the adjoining foveal or "macular" portion of the visual radiation was also destroyed. In other words, any small damage to a portion of the visual radiation may produce field defects of the shape of a more or less narrow belt stretching concentrically around the fixation point from the horizontal to the vertical meridians. In purely subcortical lesions the visual defect, or a field "rest," may never be less than a belt across the whole extent of the corresponding homonymous quadrants, from the horizontal to the vertical meridians. Only its width, that is, the extent along the radii, may vary in dependence upon the smaller or larger portion of the radiation interrupted. The wedge-shaped defects, or field "rests," of a more or less triangular shape, with a broad base at the periphery of the fields and their pointed ends at the fixation points, will be present only in

purely cortical cases, where the striate cortex itself is involved, if the cortical lesion is of a particular shape and location. Irregular homonymous field defects likewise cannot be explained by means of purely subcortical lesions. In such cases it must be assumed that the striate cortex is damaged alone or together with the radiation. Nor can small lesions in the "axial" segment of the visual radiation produce narrow homonymous field defects spreading more or less along the horizontal or vertical meridians, since each such lesion is bound to produce central or paracentral scotomas in any case extending from the vertical to the horizontal meridians, with or without the sparing of the area around the fixation points.

The frequency of the quadrantic hemianopic disturbances indicates the frequency of the injury to the visual radiation in the visual field disturbances of the cerebral origin. While the quadrantic blindness may be caused also by purely cortical lesions, if for example the striate cortex lining the upper or the lower lip of the calcarine fissure is alone destroyed (as it may happen in encephalomalacic processes), the division in the floor of the calcarine fissure between the destroyed and the normal portions of the striate cortex is hardly to be expected to follow strictly the line representing the horizontal meridians (the irregular distribution of the branches of the calcarine artery, for one, would likely preclude such a strictly "quadrantic" lesion). In purely cortical lesions or such where a subcortical lesion is complicated by a cortical one, the boundary of the quadrantic hemianopic fields separating them from the preserved quadrants is, therefore, more likely to deviate in various ways from the straight line found in cases where the visual radiation alone was partially interrupted.

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"EPILEPSY" AND LEGISLATION[1]

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INTRODUCTION

The person who suffers from seizures of any form finds himself surrounded by many limitations. Some of these are the natural consequences of his disease: he must be careful not to expose himself to certain dangers, he must rigidly stick to his routine of treatment, he must be prepared for sudden interruption of his work or other plans. Sometimes he is so confused by serial small attacks, or so drowsy with sedatives, that he is unable to work.

Other limitations spring from the prejudices of the public. A major convulsion is to most people a shocking sight, and as a result, the sufferer is apt to be debarred from work or education, indeed often from going about the streets. There is a widespread feeling that "epileptics" are not to be relied upon, that they cannot be trusted with exacting work, that they may easily break out in some criminal act. The economic handicap which these unwritten restrictions involve is enormous. The psychologic results may be devastating.

Comparatively little attention has been paid to the *legal* aspects of "epilepsy." The activities of "epileptics" are limited by law in several directions. In practically all states, "epileptics" are forbidden certain occupations, notably driving automobiles. In some states, "epileptics" are forbidden to marry, and in a few they are subject to sterilization. The problems of the right of a patient to collect damages for injuries sustained during a convulsion, and of his liability for criminal acts committed during an epileptic psychosis, are matters of common law which have received varying interpretations.

The following pages represent an attempt to point out some of the legal limitations surrounding "epileptics," and to suggest the physician's point of view toward them. The compilation of legal material is not exhaustive, and the medical opinions expressed are those of the author at present. The purpose of the discussion is to open the subject, rather than to close it.

"Epilepsy" and automobile driving. There can be little doubt that the state has the right to debar dangerous drivers from the roads. In a number of instances, the driver of an automobile has had a seizure, and an accident has resulted. The incidence of accidents of this sort is small, even though a good many people subject to seizures continue to drive, doubtless because of the protection against fits which alertness and activity usually affords. The danger to the public is far less than that due to intoxication among drivers, but it exists.

[1] The material for this article is largely derived from a book in preparation, "On Convulsive Seizures—A Manual for Patients." The author is particularly obliged to Mr. J. W. Holloway, Jr., of the Bureau of Legal Medicine and Legislation of the American Medical Association for suggestions and references.

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In most states, the application blank for a license to drive contains a question such as "Are you subject to any disease likely to cause loss of consciousness?" and a deliberately false reply makes the applicant liable to prosecution for perjury. In California, apparently alone of all the states, "epilepsy" is reportable. The law is as follows (Health and Safety Code, Section 211, 1941):

". . . The board (of health) shall define epilepsy for the purposes of the reports hereinafter referred to:

"1. All physicians shall report immediately in writing to the local health officer in writing, the name, age, and address of every person diagnosed as a case of epilepsy or similar disorders characterized by lapses of consciousness. . . .

"4. Such reports shall be for the information of the State Department of Motor Vehicles in enforcing the provision of the Vehicle Code of California, and shall be kept confidential and used solely for the purpose of determining the eligibility of any person to operate a motor vehicle on the highways of this State."

The definition of epilepsy adopted by the California State Board of Public Health is as follows: "Any condition which brings about momentary lapses of consciousness and which may become chronic, shall be considered reportable under the term epilepsy."

In other states (Connecticut and New York, for instance), if the question arises (presumably because of information given on the application form, or as a result of an accident), the Commission of Motor Vehicles may designate a physician to determine whether the driver or applicant is "epileptic."

Such laws apparently perform a useful function, and are probably in part responsible for keeping off the road those subject to seizures. Quite aside from the law, it is a widespread custom among physicians to advise patients suffering from seizures, to abstain from driving, and the advice is seldom disobeyed.

Two problems still remain, however. The first is, are there any types of seizures which do not incapacitate a person from driving? Unquestionably there are some—Jacksonian seizures involving the face alone without loss of consciousness might come in this category, for instance—but they are extremely uncommon, and in case of doubt, the patient is wiser to keep off the road.

The second is the question of recovery. According to Lennox (1), 20 per cent of patients recover spontaneously, and with proper treatment early in the course of the disease, a recovery rate of 80 per cent may be expected (2). I have not found any laws relating to "epilepsy" which take this fact into account. Most of them imply that "epilepsy" is an incurable disease, as is suggested by the definition by the Board of Health of California. This difficulty as it relates to driving is probably more apparent than real. Actually, if a candidate for a driver's license has achieved a routine of treatment which has kept him free of seizures for a period of, say, two years, he would probably be declared not "epileptic" by the examining doctor, and would then be granted a license. As a matter of precaution, it is perhaps well to advise patients not to allow the question to come up—that is, to avoid driving or apply for a license—during a pro-

bationary period of treatment, as there is no assurance that a license once refused or revoked can ever be obtained.

"Epilepsy" and marriage. In many states, the marriage of "epileptics" is forbidden by law. Such statutes exist in the following states: Connecticut, Delaware, Indiana, Kansas, Minnesota, Missouri, New Jersey, North Carolina, North Dakota, Ohio, Oregon, Pennsylvania, Utah, Virginia, and Washington (3). In Connecticut, Utah, Virginia, and Washington, marriage is forbidden only if the woman is under forty-five years of age. In North Carolina and Oregon, a medical certificate is routinely required.

A particularly severe statute is in force in Connecticut. Its provisions are as follows:

> "Sec. 6275: Marriage of epileptics and imbeciles: Every man and woman, either of whom is epileptic, imbecile, or feebleminded, who shall intermarry, or live together as husband and wife, when the woman is under forty-five years of age, shall be imprisoned not more than three years.
>
> "Sec. 6376: Procuring or aiding such marriage: Any person who shall advise, aid, abet, cause or assist in procuring the marriage of any person in violation of the provisions of section 6275, knowing such person to be epileptic, imbecile or feebleminded, shall be fined not more than one thousand dollars or imprisoned not more than five years or both." (4)

It appears, however, that such laws are not rigidly enforced. At least, the author has not been able to find records of any convictions under them. Only rarely has the presence of "epilepsy" in one partner been found adequate grounds for annulment of marriage, and then only because of fraud, if the cases abstracted by the Bureau of Legal Medicine and Legislation of the American Medical Association are representative (5, 6, 7, 8). Possibly the diagnosis of "epilepsy" is now less often made than formerly, especially among those suffering from a tendency to convulsions who are otherwise in a situation to contract marriage. Possibly also public opinion takes a more lenient view of the situation than is embodied in the laws. At all events, those subject to seizures who propose to get married would do well to seek the advice of a competent lawyer in regard to the legal status of the question at that particular time and place.

Medical, social and economic aspects of the question. To turn from the legal aspects of the question to the medical aspects, the problem of marriage may be considered separately from the problem of having children, except for the adherents of certain religious faiths, and for those who have ethical objections to contraceptive measures.

There is no evidence to suggest that sexual indulgence tends to increase tendency to attacks. Even a deliberately childless marriage may, however, be extremely unwise for patients whose earning capacity is impaired or destroyed by their disease, and who have no other income. If the attacks are not controlled by treatment, married life may be made difficult by them, especially by psychomotor episodes. The uncertainty is especially great early in the course of the disease, say within the two year probationary period. It may be easy for the well partner to consent to be childless (if this seems wise) at the outset, but it

may become more difficult as time goes on. If the decision not to have children is definitely made, the patient subject to attacks should be made sterile by surgical means, as it is unsafe to trust to ordinary contraceptive measures under the circumstances. This brings up at once the legal problem of eugenical sterilization.

"Epilepsy" and sterilization. In most states (Massachusetts constituting one exception) any person may legally have him or herself rendered incapable of procreation by means of a surgical operation, and this right is widely sought by those suffering from hereditary diseases. In certain states, duly constituted authorities may at their discretion compel the eugenic sterilization of those suffering from specified conditions, of which one is "epilepsy" (9). These states include the following: Arizona, California, Delaware, Indiana, Kansas, Mississippi, Montana, New Hampshire, Utah, Virginia, and Wisconsin. In other states, such action is mandatory by law under certain conditions in cases of "epilepsy," namely the following: Georgia, Idaho, Iowa, Michigan, Nebraska, North Dakota, Oklahoma, Oregon, Washington and West Virginia.

As a matter of experience, these laws are rarely put into effect, and then only in the severest cases upon release from an institution. The very fact that sterilization is mandatory seems to decrease the number of cases in which it is carried out. Legislation permitting certain authorities in state institutions to recommend sterilization in selected cases, as in Maine, Minnesota, and Vermont, doubtless serves a useful eugenic purpose.

There can be no doubt that in general the state has the right and power to enact and enforce eugenic legislation. How far it is wise to do so specifically in respect to convulsions, is another problem. In the present fragmentary state of our knowledge, there is room for a great variation of opinion. It seems to the author at least extremely doubtful whether preventing all those who have seizures, from having offspring, would actually eliminate the disorder in two generations, as some proponents of eugenics have hoped. A commission (10) which recently reviewed the whole question came to the conclusion that legislation making compulsory the wholesale sterilization of certain sections of the population on the basis of mere theory was both unjustifiable and impractical, but that on the other hand, legislative sanction to sterilization when recommended by qualified experts in individual instances was a considerable safeguard to the public.

Medical and social aspects of the problem. What advice should physicians give their patients in regard to having children, in states in which no legal barriers exist? The answers to this question may be taken as a critique of the legislation at present in existence. It is a difficult one, possibly affecting, as it does, the family and society as well as the individual.

Aside from the obvious economic problems to be considered, is the probability that heredity is something of a factor in all cases. Sometimes the hereditary factor seems large, sometimes small, but it should not be ignored.

There are two sets of circumstances either of which may be considered definite grounds for advising a given person not to have children. One is a history of

convulsions occurring in two or more successive generations of his (or her) ancestors.

The other is evidence that there is some tendency to seizures in the family of the prospective spouse. Under these circumstances, the likelihood that the children will be epileptic has been shown to be extremely serious.

A tendency to have convulsions can now often be disclosed by means of electroencephalography. It would be an excellent idea always to carry out this procedure in both parties when the problem of marriage comes up in regard to a person subject to seizures.

The problem becomes more debatable when it relates to a person suffering from "idiopathic epilepsy," who knows of no blood relatives with the same disorder. Unquestionably the children of such a person would run a greater risk of suffering from convulsions than the average. How much greater, it is at present impossible to predict in a given case. We do have some guidance from statistics, however, which show that about one person out of two hundred of the population at large, is subject to seizures. The incidence of a tendency to convulsions among the relatives (and presumably among the children) of patients who have attacks, is about one in forty. These statistics are perhaps somewhat deceptive, in that they include the offspring of families in which the tendency is marked, or occurs on both sides. It seems fair, however, to say that the children of a parent suffering from "idiopathic" seizures are about five times as likely to have "epilepsy" as the children of normal parents (1).

A person who has developed convulsions after a head injury or as a result of a tumor, and is relieved of them for two years or more by a surgical operation and without the use of anticonvulsant medicines, is probably entitled to consider tha this threshold for seizures is not far from normal. He has then no reason to abstain from marriage. The situation is less certain if he has blood relatives who have "epilepsy," or if he himself continues to have attacks. The statistical probability that a child of his will have them then becomes about one in sixty.

It should be emphasized again that decision in such difficult and fateful problems should be arrived at only after a careful consideration of the individual circumstances, including the economic position of the prospective pair, the family histories, laboratory tests, and the effect of treatment. The outlook should be discussed with complete candor by both parties involved, with an experienced physician. It is always wise to leave a considerable period—six months at the least, more in early cases—for all concerned to think the matter over, and watch the progress of symptoms and treatment. Eventually, of course, the decision rests upon the prospective partners (in states in which there are no legal impediments).

The point of view in regard to the marriage of those subject to convulsions, which has just been presented, differs considerably from the accepted medical doctrine of a generation ago, which was that "epileptics" should never marry. It is quite possible that further advances in knowledge will alter the situation still more. If, for example, there should be improvement in our methods of determining the degree of constitutional susceptibility to attacks, in those suffering

from them and in unaffected individuals, the problem would become much clearer. A change of sentiment might easily take place also if methods of treatment become more effective. An interesting parallel is furnished by the history of diabetes, in which heredity is as definite a factor as in the tendency to seizures. Marriage was formerly considered out of the question for diabetics. Now that an effective treatment is available, the economic hazard has become one which can be estimated, and the possibility of having a child who may develop diabetes no longer seems calamitous.

Legal liability of "epileptics"; legal aspects of employment of "epileptics" No general rule can be laid down concerning liability for damage done to the person or property of others during an attack. The existence of a psychic equivalent seizure has apparently seldom been used as a legal defense, perhaps evidence that misdemeanors rarely occur during seizures. The fact that a person suffers from convulsions does not incapacitate him for making contracts, or making a will, nor relieve him of the responsibility for his actions. A number of illustrative cases have been abstracted for the American Medical Association (11, 12, 13, 14, 15, 16, 17).

Suits for damages on account of injuries sustained during convulsions, are sometimes brought against employers under Workmen's Compensation Laws. They have sometimes been decided for the plaintiff, sometimes for the defendant, depending upon the circumstances of the situation. In general, an employer is unwise to hire or keep a workman known to be liable to convulsions, in surroundings in which an attack is likely to lead to serious injury. On the other hand, the employer has not been found liable for injury incurred during an attack in a situation involving no special hazard; for example, a sidewalk (18, 19, 20, 21, 22, 23, 24, 25).

The need of a legal definition of "epilepsy". The legal situation would become much clearer if there were a generally accepted legal concept and definition of the term "epilepsy," which is the one almost universally used in the legislative acts and court precedents which concern us here. Dictionaries usually define *epilepsy* as "a chronic disease characterized by convulsions" or words to that effect—a rigid and inadequate definition considering the complexity of the situation. The definition given by the State Board of Health of California has already been considered; but it should be noted that reports of cases under this definition are to be "used solely for the purpose of determining the eligibility of any person to operate motor vehicles on the highways of the state."

As has already been pointed out, many people have one or several convulsions as infants, yet grow up to be apparently normal. Others have seizures only after some head injury or other unusual circumstances. Still others have a few seizures and then no more, either because of spontaneous cessation or as a result of proper treatment. The questions—What constitutes a seizure? How many seizures over how long a time constitutes a chronic? What evidence is required to show that the tendency is hereditary in a given case?—are extremely difficult to answer.

It would seem that a proper legal conception should take into account the

presumptive intent of the law under which it is to be applied. The following attempts at clarification of the issue are put forth as being reasonable in attitude and practical in application. They have not been specifically tested in court, but seem to be in accord with the legal rulings which have come to the author's attention.

The laws specifically affecting "epileptics" fall, in general, into three categories: those limiting the employment or activities of the sufferer, those limiting his liability or the liability of others toward him, and those affecting his right to marry and procreate.

Laws of the first category are usually limited to a prohibition against driving an automobile, but the same principle could or should be extended to such occupations as running an elevator, driving a street car or train, or piloting a boat or aeroplane, where lives would be endangered by a sudden lapse of consciousness.

The intent of such laws is obvious: the term "epileptic" is used in the sense of "one who is particularly apt to have a lapse of consciousness under dangerous circumstances." Since any apparently normal person may have his first convulsion or fainting attack at any time, it would seem further that the intent of such laws is to avoid unreasonable risks. In estimating what risks are unreasonable, it would seem wise to take into account the actual circumstances of the specific employment, the history of the individual case, including the time of onset of the first attack, the interval since the last attack, details of medical examination including electroencephalography and the results of treatment. These (and other) laws appear to have been framed on the assumption that the condition "epilepsy" is a permanent and irremediable one. If it is shown that in fact the symptoms have long since disappeared spontaneously or following treatment in a given case, it would seem that the assumption is invalid and that the laws do not necessarily apply. As a tentative standard, satisfactory in the author's experience, patients who have been free of attacks for two years may ordinarily be considered to run no unusual risk in driving a pleasure car. Aeroplane pilots and drivers of public vehicles should doubtless be held to stricter standards.

No statutory laws dealing specifically with the liability of an individual for damage he might cause during an attack, or with the liability of others toward him, have come to the author's attention. The issues involved in any particular case would seem to rest on the criteria suggested in the last paragraph, plus a history of events and the results of examinations since the occurrence of the incident in litigation.

The legislative restrictions on the marriage of "epileptics" and the various sterilization laws clearly rest on a different basis. The question is obviously not one of danger to life or property. Nor is it an economic one; it is probably unconstitutional to forbid marriage or procreation in the individual case without due process of law on the grounds that the parties concerned or their offspring might become a charge on the public. The underlying assumption is that "epilepsy" is hereditary; that in procreating, an "epileptic" runs an unreasonable risk of transmitting his disorder to succeeding generations. The average statis-

tical risk of having a child who will suffer from seizures, and the increased statistical risk faced by those subject to attacks, has already been considered. Justified or not, such legislation doubtless applies to cases in which a hereditary tendency to seizures is obvious in the patient's parents or immediate relatives. They might reasonably apply also to cases in which relatives can be shown to have cerebral dysrhythmias (as revealed by electroencephalography in competent hands).

As a corollary, such laws might be assumed *not* to apply to categories of cases in which heredity appears to play a small part or none at all—for example, in cases in which the patient has had convulsions only as an infant, or only following an electric shock, with no family history. Cases in which the seizures have developed following an injury or the growth of a brain tumor, and are relieved by removal of the lesion, probably belong in the same category. Whether the same principle applies to cases relieved of convulsions by other types of treatment, or to individual cases in which no hereditary influence is apparent, is open to question. Electroencephalographic examination of the patient and his parents would be relevant.

In any situation in which the term "epilepsy" applied to an individual tends to restrict his rights or liberty of action under the law, it would seem justifiable to assume that the application of the term were legal only after due process of law had been invoked—that is, after a hearing in court. It is not clear how such hearings should be initiated.

A review of the literature and contact with a good many patients leaves the author with the impression that laws of the type under discussion are widely disregarded, both by the public and by the courts.

Meanwhile, the fact that the term "epilepsy" has definite legal implications in many states, suggests that its use by physicians should be strictly limited to those cases which obviously come under the statutes cited. Better still might be to drop the term entirely from medical literature. The situation is in many ways parallel to that of the term "insanity", which now represents a legal, rather than a medical conception. The word "epilepsy" is, however, more difficult to replace, as no substitute has as yet become widely accepted.

SUMMARY

1. A survey of the legal limitations surrounding patients suffering from seizures is presented.

2. In many states, there are statutory restrictions on the rights of "epileptics" to drive automobiles and to marry. In some states, sterilization of "epileptics" is permissible, in others mandatory.

3. There are certain principles in common law which are often applicable to the legal responsibility of "epileptics" for their acts, and to their testimentary capacity. The legal liabilities of employers for accidents to "epileptics" is discussed.

4. Some criticism of existing legislation is offered, and a medical point of view toward it suggested.

5. Various definitions of the term "epilepsy," applicable to various legal situations, are suggested.

6. Since the use of the term "epilepsy" involves certain legal implications, it is suggested that its medical use be restricted to a minimum.

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THE SIGNIFICANCE OF THE METEOROLOGIC ENVIRONMENT IN THE ETIOLOGY OF PSYCHOTIC EPISODES[1]

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Adolf Meyer's Psychobiology emphasizes with the prefix *psycho* "the devotion to the reactions of the unitary organism in the study of man as a person, clearly within the general framework of biology" and Muncie illustrates "the essential elements of full fledged mentally integrated activity of the total organism." Thus, the organismal nature of native assets, instinctual drives, endowments of acquired skills and habits, and basic variability in moods, imagination, and reasoning, is unfolded as a modification of constitutional structural inheritance through growth (biology), by various situational life experience factors (psychology), and their integration by the cerebral hemispheres (anatomo-physiology). When Meyer replaced such purely hypothetical "behind the scenes" etiologic factors in psychiatry by his formulation of psychopathologic disorders as an experiment of nature, in which the genetic dynamic considerations described the factors favoring or obstructing parergasic or thymergasic modifications upon exogenic, organogenic, neurogenic, psychogenic, and constitutional causes, Meyer opened wide the doors of the psychiatric work-shops inviting thereby cooperation from all laboratories of science. W. F. Petersen, of the University of Illinois, has studied human beings day by day for years from biologic, constitutional, biochemic, and clinicopsychic viewpoints. He has demonstrated in kinetic graphs that the autonomic integration of biochemistry and of psychic reactions is never static but is in a constant rhythmic swing varying in intensity in different body types. The integration or disintegration of physical, biochemical, and psychic variants are clearly influenced by changes in the weather. To the uninformed, such a correlation may seem assumptive, and its objectivity may be questioned.

Dr. James Mann, a member of the Massachusetts Medical Society, wrote in his Medical Sketches of the Campaigns of 1812, '13, '14, "While we consult practical authors, some regard should be had to climates and local situations. Geography and topography are particularly important to the physician and surgeon, to become acquainted with the connection which subsists between climates and constitutions in exploring the manner diseases are affected thereby, inasmuch as local situations and climates produce varieties in the human constitution, which diversify the forms of diseases. Experience has taught us, the health of men is more or less affected by change of climate." In Mann's Boylstonian Prize Essay (1800) it is stated: "Cold and sudden transitions of weather from hot to a colder state of atmosphere are considered as exciting causes of dysentery. Great variations of weather cooperate with all the hurtful agents during every season of the year." Mann describing the weather conditions writes in his Observations on the Winter Epidemic of 1815–16, the Peripneumonia Notha at Sharon, Massachusetts. "After a very cold January and part of

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February, the transition from cold to very warm was sudden. The change in March from very pleasant to severe cold was great and these sudden variations continued into May. These transitions are believed to have been one cause of the epidemic." And the keen clinician Mann asked: "Atmospheric influences are out of the bounds of our knowledge; and were we able to comprehend their nature, could we by any means control their powers so as to obviate their effects upon the human constitution? While the animal creation is fortified by nature against the varying seasons and more sudden transitions of weather, man is endowed with reason to direct him, how to avoid their deleterious effects."

It is not difficult to compile from medical writings or commentaries a large number of aphorisms (terse, pointed sayings, embodying an important truth in few words), which relate to climate and weather in its relationship to health and disease.

European psychiatrists analyzed their clinical and laboratory records with the reactivity of selected psychiatric case material. I shall concern myself with certain phases of the work of European psychiatrists, with considerations of the regional meteorologic environment and a graphic explanation of the meteorobiologic observations as related to clinical facts in the manner given by Petersen.

Normal mental processes require the maintenance of proper vascularization. Hippocrates called particular attention to mental disturbances caused by interference with vascular supply resulting from undue spasm or undue dilatation of the blood vessels ("Sacred Disease"—"Breaths"), and to changes in the mental functions by undue hydration or dehydration of the tissues. He likewise stressed the all important role of the meteorologic environment in mental function and psychic reactivity.

Petersen, who has discussed this subject at length, has sought to integrate the psychic status with changes in the meteorologic environment.

In his studies it became evident that the onset of disturbance in the schizophrenic-leptosome is associated with lowered blood pH, lowering of blood pressure, blood sugar, etc., designated by him as the COD phase (acid phase: with increased catabolism and oxidation and with vascular dilatation to accommodate the demand for increased oxygen). The onset of hypomania is usually associated with the opposite phase, i.e., with a period of relative sympathicotonia, with an increase in blood pressure, a relative alkalosis (the blood pH, blood pressure, and blood sugar becoming increased and the carbon dioxide content decreased), and designated as the ARS phase (anabolism, reduction, and vascular spasm). Inasmuch as all biological balances are interrelated, changes can be observed in the ratio of calcium to potassium, in the redox potential, in the calcium-phosphate ratio, in the cholesterol (lipoid) level, in the water balance, nitrogen balance, etc. (Petersen 1, 2).

The conclusion can be drawn that given a deficient cerebral substrate, functional inadequacy follows when the *milieu interieur* swings beyond the range of adjustment for the inadequate tissue. Dysfunction occurs in the manic-depressive individual with the development of undue alkalosis and anoxia (ARS phase), and in the schizophrenic individual with undue acidosis (COD phase) corresponding biologically to the fatigue state of normal individuals.

In its simplest expression, the change in mood that is illustrated by the onset of

an acute psychotic episode is well revealed in a recent case record presented by Simon (3). The abbreviated case record is as follows:

Case 1. A 38 year old white woman, was admitted October 16, 1936. Family history was negative for nervous and mental disease. Birth and early development were normal. On October 13, 1936 the patient developed mental symptoms. She became disturbed, neglected her work, thought she was going to die, and complained of pain in the stomach; she wanted to go outdoors at two o'clock in the morning; she said someone was going to burn the house down, stared into space, and so was committed. Diagnosis: Dementia praecox.

When we examine the meteorogram of the time, it will be evident that an acute episode began with a barometric crest and with a period of lowered environmental temperatures. This onset coincides, therefore, with the passing of a cold

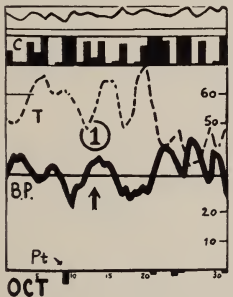

FIG. 1. Meteorogram illustrating above the wind velocity, the upper black columns the degree of cloudiness, the dotted line the daily mean temperature, the heavy black line the barometric pressure; precipitation is indicated by the black columns below the date line. The period is October 1936; the acute episode recorded is October 13.

air mass which in turn should have resulted in an increase in blood pressure, a relative anoxia in the peripheral and cerebral tissues, the gradual production of intermediary acid products of metabolism (capillary active substances, such as histamine, ketone bodies, etc.), and undue fatigue (COD phase of the tissues).

It may be asked: What about the homeostatic capacity of the organism in such a case?

Homeostasis is maintained by endocrine, chemical and nervous reflex actions. The body is usually in an unstable equilibrium, with adjustments necessary for nutrition, work, digestion, emotion, trauma, sunshine and particularly to air mass (temperature, pressure, humidity, ionization, etc.). Reaction to any one of these effectors must obviously involve change in the chemical equilibrium and the degree of this change will depend on the energy impact as well as the periodicity and frequency. The change is reflected in both the pH and carbon dioxide content, in water content, lipoid content—in fact, any measurable element of serum or tissue fluids. The only reason this change is not commonly considered is simply the fact that few investigators have taken the trouble to study its day by day pattern.

However, detailed chemical analysis of the blood at frequent intervals yields more information with regard to the total metabolic state of the body than was formerly thought possible.

The passage of a cold air mass is associated with a complete reorientation of the organic status. The characteristic "defense" or "alarm" reaction finds its major expression in the shutting off of the periphery of the body against the outer world. It is in part associated with a sympathicotonia, including an increase in blood pressure, blood sugar, and a decrease in protein concentration of the blood and in the oxidative rate. The vasoconstriction involves, in varying degrees, the pelvis, cerebral cortex, and spinal cord—and in these regions a relative anoxia exists. This phase has been described as Petersen's ARS phase (spasm of the smooth muscles). Selye termed it "alarm" reaction; and Pal described it as a "pressor crisis."

As compensatory mechanism, a complete reversal now occurs (initiated largely by the products of the anoxia, acid in character, and including carbon dioxide in increased amounts, lactic acid, ketone bodies, histamine, etc.). With this compensatory phase there is a lowering of the blood pressure, blood sugar, and pH level, and an increase in cholesterol.

GJESSING'S OBSERVATIONS

It is perfectly simple to make meteorobiologic correlations such as these and to follow along the underlying biochemical observations. Possibly because of the rather laborious procedure involved, his work has so far not been repeated by others, although the growing interest in psychotic changes as related to constitutional status warrants further work along these lines either to confirm or to refute his findings and conclusions.

Rather than merely repeat his work, we have turned to a different line of examination, namely, the employment already of data available in the literature, where clinical and biochemical observations were made by others and correlating the clinical changes with the meteorological conditions. It is this line of procedure that is recorded in this paper. We turn first to observations made in Oslo, Norway. It is to Gjessing (4) that we are indebted for the first detailed day by day accurate dating of events and studies of the clinical and biochemical alterations of psychiatric patients (catatonic stupor or excitement). Gjessing was not interested in meteorological associations, but his published material gives us the opportunity for an integration which is not only striking but conclusive. We have, moreover, obtained the meteorologic data for the periods during which Gjessing's patients were studied, so that we need merely turn to the meteorology of these periods to be able to assign the cause for the changes in the total metabolic state of the patient revealed in his biograms as well as the psychic upset.

The careful studies of Gjessing reveal that catatonic schizophrenics retain nitrogen phasically, and that they discharge the accumulated nitrogen upon recovery.

Case 1. The patient was born on October 14, 1903 and was a printer's apprentice. The father's brother was mentally disturbed. The father was of athletic, the mother of pyknic habitus, and cyclic. As a boy he seemed peculiar in many ways, very stubborn, moderately able in school. He was industrious, interested, and capable, but had no companions. In April, 1922, there was a sudden change in mental qualities when he became inattentive, complained of loss of memory, and inability to work. He made futile efforts to work. He talked to himself, considered himself watched and subjected to persecution. He remained in bed five weeks and then took up his work again. On June 23, 1922, he became suddenly disturbed (Episode I): very talkative, self-conscious, irritable, threatening, and had delusions of persecution, and increased irritability during the course of the next few days. Two to five such episodes recurred on June 17, 1926; January 5, 1929; June 11, 1930; and July 4, 1934

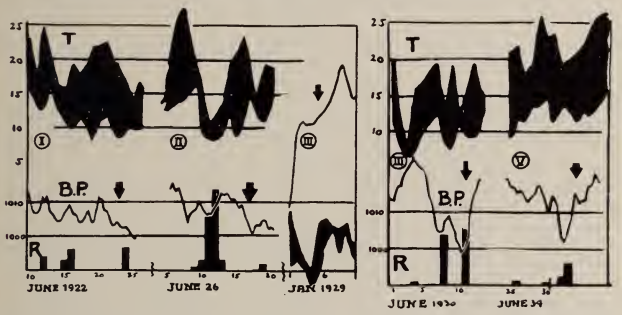

Fig. 2. The onset of acute psychotic episodes in Gjessing's Case 1. Upper curve maximum and minimum temperatures for Oslo, in degrees centigrade. Continuous curve indicates barometric pressure. Arrows point to dates of onset of psychiatric episodes 1, 2, 3, 4, and 5. Precipitation indicated by the black columns.

Examination of the meteorology that corresponds to these five episodes reveals the following:

The first episode (arrow) of June 23, 1922, occurred at a time when environmental temperatures were rapidly declining, when barometric pressure had decreased materially during the course of three days from a crest on the twentieth of the month. The attack presumably occurred at an air mass interface, because on the twenty-fourth of the month there was marked precipitation.

The second episode of June 17, 1926, again occurred at a time when barometric pressures had reached a low level (arrow); but at this time temperatures declined sharply from a high on the preceding day. (Note a major cyclonic interface just preceding, i.e., June 11 and 12.)

The third episode of January 5, 1929, occurred when barometric pressures had increased very markedly from January 1, with lowest temperatures reached on the fourth of the month. At this time, there was a sudden shift toward increasing temperatures, but at the same time, an increase in barometric pressure occurred after a transient arrest of the trend.

The fourth episode of June 11, 1930, occurred with the passage of a sharply

demarcated polar front, after unusually low barometric pressures on the preceding day; there was marked precipitation and temperatures had decreased.

The final episode also followed a period of unusually low barometric pressure when there had been rain, and the patient was admitted to the hospital (July 4) at the succeeding barometric crest.

In each of the four instances, one observes an acute clinical disturbance in association with, or increasing in the wake of, environmental disturbances of considerable magnitude. The patient usually became disturbed at a period of low barometric pressure after the passage of a cold air mass. Biologically, the situation would correspond to a COD phase of considerable magnitude (increasing acidity, lowered blood pressure, increasing capillary permeability, increasing metabolism, etc.).

We turn next to Gjessing's Case 4, with the following history:

Case 4. The patient was a student, born in 1911. Three sisters of the father were nervous and a child of one of them was schizophrenic. His paternal grandfather was nervous in his youth, his brother and a son were both schizophrenic and died in institutions. The grandmother was well, but a son of her sister was schizophrenic. The great grandfather was in an institution because of melancholia.

The boy was normal until puberty; he was one of the best students in the school. Then there followed a gradual change in character pronounced at the age of 17. He became reserved and irritable, stubborn, and disagreeable. In school he became distraught, with lessened ability to concentrate; began to be irregular in his attendance of the high school, got low grades and failed in his examinations. He entered the University, but was a poor student; he was occasionally alcoholic. During 1931 and 1932 his moods were very variable, and he was depressed and irritable, but at other times, overcompensating and pugnacious.

On December 2, 1932, sudden extreme psychomotor irritation necessitated admission to the Oslo Psychopathic Institute.

Gjessing published numerous graphs detailing the clinical and biochemical observations in this case. We are taking the liberty of reproducing some of these.

A characteristic chart (Gjessing's figure 11) of the original paper is here reproduced (fig. 3) in which the upper curve S and C indicate the psychic and motor status of the catatonic patient. Curve 9 illustrates the nitrogen intake and output, Curve 10 the ammonia nitrogen, Curve 11 the titratable acid, Curve 12 the acid-base balance, Curves 13, 14, and 15, the sulphur, phosphorus, and chloride output of the urine; Curve 16 the urine volume and finally the weight curve of the patient is traced. Figures 4 and 5 are explained by their captions.

We turn next to Figure 6, in which the relation of the leucocyte count to the change in blood pressure is indicated and where we can finally examine the relation of these changes to the meteorological conditions of that time. If the reader will first examine the blood pressure crests which have been numbered 1–16, he will note that crests are found that follow the curve of the leucocyte count, and by reference to the corresponding periods in the meteorogram, he will note that an increase in blood pressure and leucocyte count have been associated with a decline in temperatures, and with an increase in the barometric pressure.

In figure 7 the heavy arrows point upward to five periods of onset of psychic

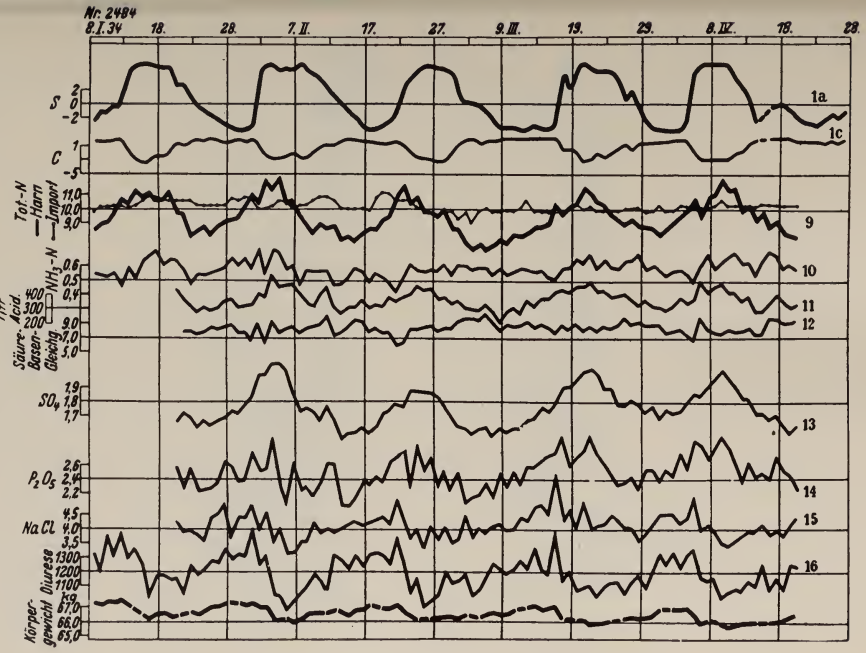

Fig. 3. Reproduced from the original graph (Gjessing's text, fig. 11)

excitation. The arrows have been carried through from the graphs indicating the oxygen consumption, respiratory quotient, and pulmonary ventilation, and have also been carried through the meteorogram of that time. It will be noted that major changes occurring in the psychic reaction of the patient are definitely associated with periods when stimulation has occurred as the result of periods of increased cold (and usually when change occurs from a period of low barometric pressure) or that such changes in the psychic reaction follow periods of unusually high barometric pressure. Minor periods of cold have been lettered a, b, c,

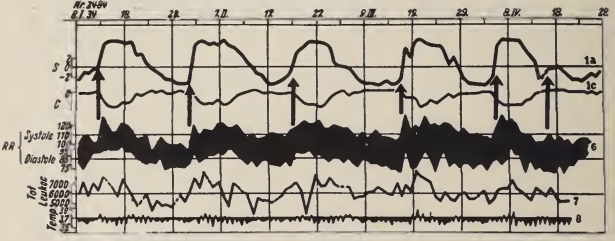

Fig. 4. Systolic and diastolic blood pressure and leucocyte count from Gjessing's text figure 10 with superimposed curves indicating psychic status. Upturned arrows indicate beginning of periods of excitation.

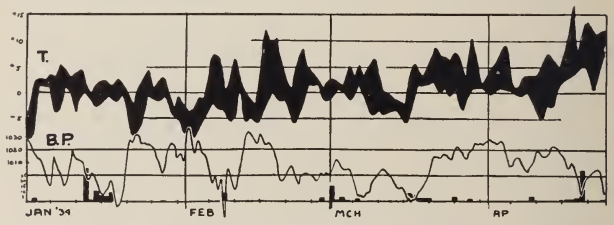

Fig. 5. Oslo meteorogram for January to April 1934. Upper curve maximal and minimal temperatures in centigrade. Lower curve, barometric pressure. Precipitation indicated by the black columns.

d, and e on both the temperature and the barometric pressure curve, and it will be noted that even these minor changes usually find reflection in the curve of psychic reactivity.

While it is by no means absolute, the continued activation or slight reactivation of psychic activity, indicated in Curve S and lettered a, b, c, and d, is seen to have reflected meteorologic episodes resulting in the stimulation of the patient as a whole. It is impossible to verify this in any statistical fashion, but the deduction is permissible.

The initiation of the acute psychiatric episode in this case again associated

with periods when vascular spasm (associated with the passage of cold air masses) is followed by a COD phase. When once initiated, further environmental alterations are reflected in an increase in the psychomotor activity until the threshold levels are raised and a catatonic or stuporous phase stage follows when further stimulation is no longer effective. This resistant stage then persists for approximately ten days (this is the normal period of biological reorientation) and then the nervous system again appears to become sensitive. Some of the underlying mechanisms involved here have been discussed in detail by Petersen.

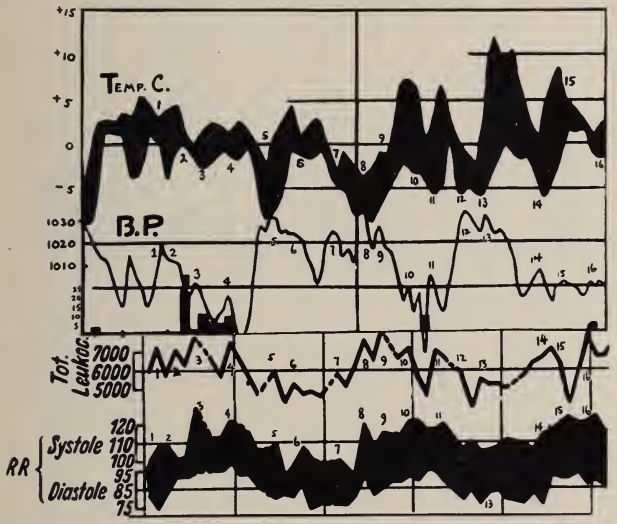

FIG. 6. Oslo meteorogram extended over curves of blood pressure and leucocyte count of Gjessing's case. Periods of increase in systolic blood pressure in leucocyte count, etc., have been numbered 1–16 and corresponding periods of decreasing temperature level and increasing barometric pressure are numbered on the meteorogram.

SCHEID'S OBSERVATIONS

Scheid (5) published a monograph *Febrile Episoden bei Schizophrenen Psychosen* in 1937. It provides us with a series of dated episodes in psychiatric patients and, in addition, presents a detailed study of biochemical alterations similar in character to those which Gjessing has published. In view of our interest in the meteorologic association of the psychiatric episodes, we have made a graph of the meteorology of Munich at that time and can now study the interrelation that may have existed.

Case 1 (fig. 8) concerned a fatal febrile catatonia, hemorrhagic in character. The patient, a woman, 37 years of age, apparently had been well and never disturbed, apart from minor irritability before menstrual periods. On December 1, 1934 (1) the patient was de-

livered of a dead baby, and fourteen days after this event rather severe uterine bleeding occurred, associated with a febrile urticarial exanthem (2). Three weeks after delivery, a psychotic disturbance occurred (3); the patient became quiet, participated very little in the Christmas festivities, found it difficult to concentrate, became nervous, irritable, etc. The entire process cleared up in approximately five weeks.

Four weeks later the urticarial exanthem with high fever recurred, together with a renewal of psychotic manifestations. The patient died in a state of severe cyanosis on March 25, 1934 (4).

The selection of these case records of Gjessing and of Scheid might seem, from our point of view, particularly useful because of the recent discussion of this material by Stokes (6). It is not my purpose to discuss in detail the chemical

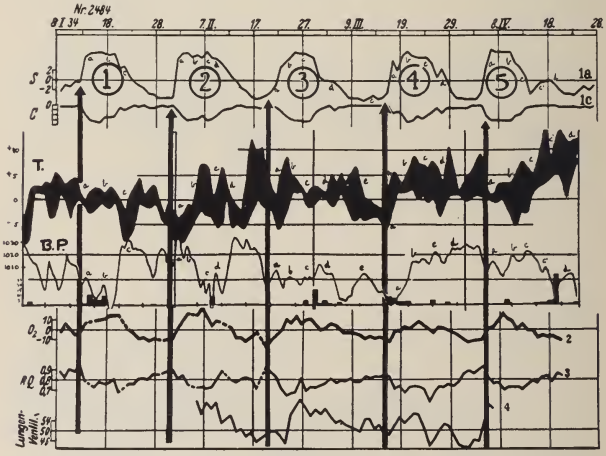

Fig. 7. Meteorogram interposed between Gjessing's graph indicating psychic status and (below) the oxidation respiratory quotient and pulmonary ventilation of the same patient. The effectiveness of change in environmental temperature indicated by the lettered episodes over the curve of environmental temperature and the barograph. Similar letters under the curve of psychic status.

studies published by Gjessing or Scheid. The synchronization of the metabolic phases of man, normal as well as abnormal, with meteorologic events has been studied by Petersen ("The Patient and the Weather"), and the general significance of phase pendulation for the psychoses is discussed by Stokes.

When we examine the meteorograms, it will be noted that the stillbirth occurred with a period of relative cold and high barometric pressure;[2] this was followed by a continuous decline of barometric pressure until the fifteenth of the month;

[2] The effect of environmental cold and meteorological disturbance on stillbirths and the onset of delivery has been discussed by Petersen and Milliken in "The Patient and the Weather" Volume I, Part 2, Chapter VIII, Page 601.

then barometric pressure increased sharply. This critical period around the fifteenth of the month was reflected in uterine bleeding (minimal environmental temperatures of the time) which presumably occurred either because of undue increase in arterial pressure or the converse, a period of unusually low blood pressure and passive hyperemia (2). The urticaria of that time also reflects the change in vascular status. The onset of the first episode of psychosis apparently coincides with the next severe fall in environmental temperature (3). It is not possible to date the onset of the succeeding episode of psychosis, but death occurred on the twenty-fifth of March with a barometric crest and immedi-

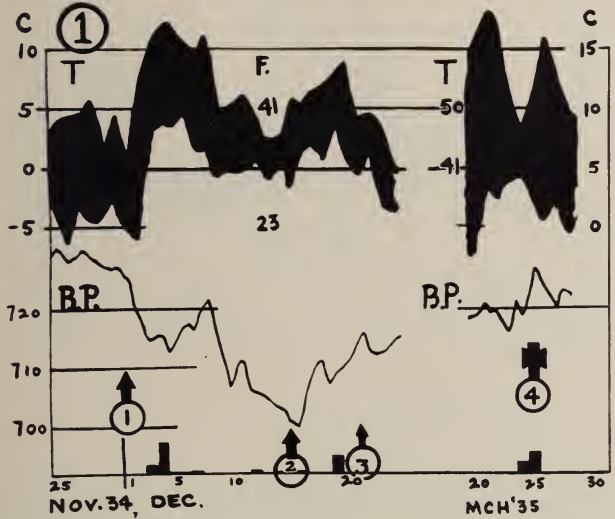

FIG. 8. Meteorogram to illustrate the association of meteorological changes and the clinical episodes in Scheid's Case 1

ately in the wake of low temperatures (4). There was precipitation at this time. As has been discussed previously, a patient who is critically ill becomes more and more susceptible to environmental alteration, and death may follow during periods of declining temperatures or immediately in the wake of such periods.

Case 2 (*fig. 9*) concerned a male patient, 33 years of age, who became suddenly ill on December 13, 1935 (1). He felt bad, thought that he had been poisoned, and that he was becoming insane. The same evening he began to be violent and believed that he was dying. The next day he was quiet and the following night again showed hypomania (2). At this time, he had fever and was sent to a State Hospital on December 17, and died on the day of admission (3). Autopsy revealed hyperemia of all parenchymatous organs. Hypostasis of both lungs. Small hemorrhages in the mucosa of the stomach, rectum, and kidney pelvis. Pulmonary emboli of main artery of right lower lobe.

When we examine the meteorogram we again note a definite meteorological association, insofar as the onset of clinical symptoms which occurred shortly after a very high barometric crest, but at a time when temperatures were declining sharply (1). The day following, with increasing environmental temperatures and fall in pressure the patient apparently improved, only to become more disturbed with the following slight increase in barometric pressure (2). Death occurred (3) with the crest of environmental temperatures and sharply declining barometric pressure (passage of cyclonic crest).

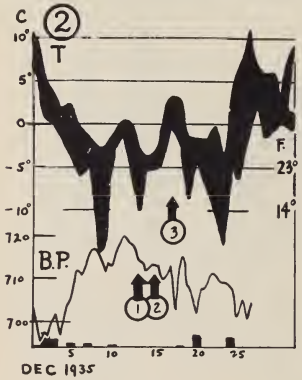

Fig. 9

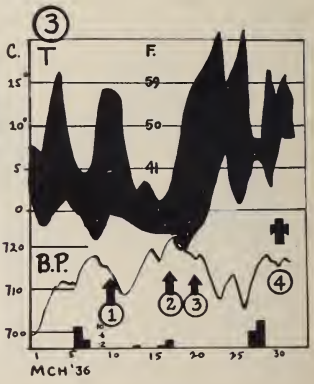

Fig. 10

Fig. 9. Meteorogram illustrating the clinical episodes in Scheid's Case 2
Fig. 10. Meteorogram illustrating the clinical episodes in Scheid's Case 3

Case 3 (fig. 10) concerned a woman, 20 years of age, who had taken a fortnight's excursion during February 1936. During this time she suffered from insomnia and immediately afterwards developed the notion that she had been poisoned and in connection with these delusions was admitted to the Psychiatric Institute on the 10th of March 1936 (1). During the first few days, she was considerably excited. On the 17th a "butterfly" erythema of the face was noted (2); the next day—cyanosis became evident. This improved somewhat by the 20th of the month at a time when the pulse became smaller (3). After this, progressive cyanosis again developed and the patient finally died on the 30th of the month (4).

From the meteorogram of the time, it will be noted that the disturbance of the patient began with a period of steeply increasing barometric pressure which extended from the 1st to the 8th of the month. She was admitted on the 10th (1). During the period from the 10th to the 17th, the patient developed the described erythema (basically a vasomotor disturbance), and this, too, it will be noted occurred with a sharp fall in temperature and increase in barometric pressure (2). There now followed some improvement with falling pressures and increase in temperature (3). Then, beginning with the 24th of the month,

there occurred an increase in barometric pressure, and a temperature decline, the patient became increasingly disturbed, and death occurred at the time of a barometric crest (4).

Case 4 (*fig. 11*) involved a febrile, cyanotic form of psychosis, episodial in character (no drug intoxication), in a female 28 years of age, who had revealed some psychotic traits ever since puberty. About the middle of September 1932 (1) the patient began to sleep poorly, was markedly fatigued, and on the nineteenth of September (2) suddenly became disoriented. She was admitted to the institution on September 24 (3). At this time, there was definite cyanosis of the lips and extremities, and the pulse was markedly increased. She became hypomanic on the same day. On the morning of September 26 (4) the patient presented clinical evidence of vasomotor collapse. The corneal reflexes could hardly be elicited, the patellar and Achilles reflexes had disappeared. The patient was quite cyanotic and seemingly moribund. Treatment with Euphyllin and calcium appeared to afford improvement with ultimate recovery.

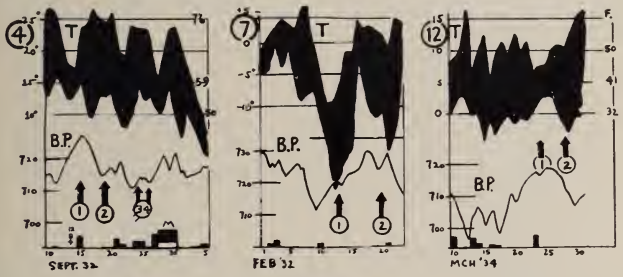

Fig. 11 Fig. 12 Fig. 13

Fig. 11. Meteorogram illustrating the clinical episodes in Scheid's Case 4
Fig. 12. Meteorogram illustrating the clinical events in Scheid's Case 7
Fig. 13. Meteorogram illustrating the clinical events in Scheid's Case 12

On the meteorogram, the clinical episodes are indicated by arrows 1–4 and the menstrual period is indicated by the lettered days M. When we examine the meteorogram, it will be noted that the period of insomnia (1) began during a time when barometric pressures increased very markedly.[3] The first acute episode on September 19 (2) occurred with a change in the air mass, presumably with the passage of a polar front. A similar situation obtained with the next episode (3) at which time she was admitted to the hospital. The subsequent vasomotor collapse (4) occurred when, as a result of prolonged vasoconstriction, tissue anoxia resulted and blood pressure fell to low levels. Accentuation of symptoms would be expected to occur at times of cyclonic passage (lowered barometric pressure), and in this instance the effects of both factors were in turn enhanced by the endocrine status of the patient (premenstrual phase).

[3] Increasing restlessness and insomnia is frequently observed with relative vasoconstriction (ARS phase) associated with increasing cold.

Case 7 (*fig. 12*) concerned a female, 42 years of age, who had previously been cheerful, sociable, but rather sensitive. Disturbance began in July 1927, when she became depressed. On the whole, she made fair adjustments until early in 1932. On February 13 she had to be admitted to the Psychiatric Institute (1). At this time, she was somewhat cyanotic and catatonic. On February 20 (2) a marked change occurred in that she became violently disturbed, the pulse was small, cyanosis was more pronounced.

When we examine the meteorology corresponding to these two dates, we note that in both instances we are dealing with clearly defined polar events with unusually low temperatures.

Case 12 (*fig. 13*) concerned a female, 31 years of age, who had difficulty in adjustment for quite a number of years and during the two years preceding her admission to the Psychiatric Institute had pronounced delusions. She was finally admitted (November 20) and diagnosed: paranoid hebephrenic type of psychosis. On February 28, 1934 stupor intervened. She no longer reacted to sensory stimulation. At the same time, there was very marked seborrhea of the face. Examination of the patient's temperature curve indicates that on the twenty-fourth of the month, a sudden but transient elevation occurred. On the twenty-eighth, with the onset of stupor, her temperature again increased to 39°C. and continued so for several weeks.

When we examine the meteorogram of the time, we again observe that the entire episode occurred in association with a major barometric crest, the first febrile episode (1) occurring immediately in the wake of a cold wave of moderate degree and following precipitation on the twenty-third of the month. The actual onset of stupor occurred with minimal temperatures but declining barometric pressure (2).

Case 17 (*fig. 14*) concerned a young man, 19 years of age, who first complained of a feeling of fatigue in August 1936 and by the first of September (on admission) was suffering from delusions, remained in bed, grimaced, and was hyperactive at times. After a week, his condition improved. During the middle of October, there was a recurrence which lasted about a week, and with this there was a febrile reaction, with temperatures reaching 38.6°C. A third episode ("Schub") occurred on November 4, 1936.

The metabolic alterations observed during this and the subsequent episodes 4, 5, and 6 can be followed in Scheid's comprehensive graph.

Since we are interested here only in the meteorological associations, we shall omit discussion of Scheid's interesting metabolic studies. The onset of episode 3 followed immediately in the wake of a striking meteorological event. A barometric crest was reached on October 30. With this, there was maximum cold; followed by a cyclonic front with precipitation of 31.4 mm. A barometric crest now followed and with this a psychic upset. It should be noted that the whole episode was associated with a period of unusually low barometric pressure (circle).

The onset of episode 4 is identical. A maximum period of cold was reached by November 28. Another barometric crest followed on the thirtieth of the month and with the succeeding period of very low barometric pressure (circle), the patient became disturbed. Again there was marked precipitation at this time.

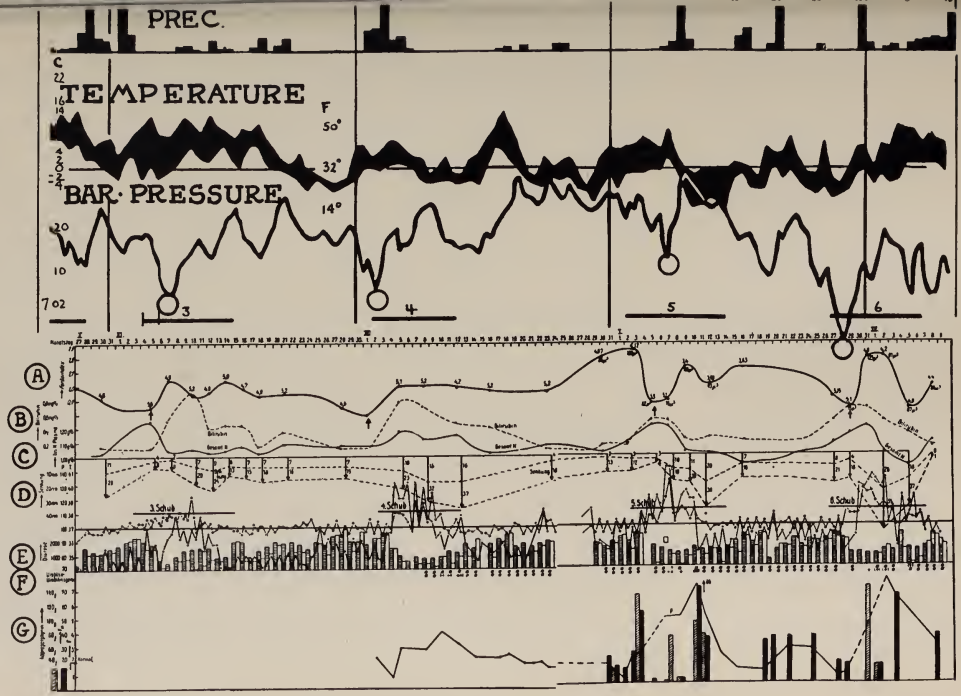

FIG. 14. Meteorogram for Munich for the period from October to the middle of February, covering the psychiatric episodes 3, 4, 5, and 6. Subtended below is Scheid's graph from which the biochemical records can be followed.

The fifth episode presents the same sequence, with maximum cold on the twenty-ninth of December. Another barometric crest was reached on the thirty-first and with the decline, the patient became disturbed. In this instance, the lowest period of barometric pressure was in evidence several days after the onset of the disturbance.

The sixth episode was initiated under slightly different environmental conditions. A major barometric crest was reached on the twenty-third of January. Then pressure declined progressively. Here again psychic disturbance was associated with a period of unusually low barometric pressure.

As we survey the graph only superficially, it becomes obvious that the four episodes are associated with periods of unusually low barometric pressure, succeeding periods of cold.

DISCUSSION

We have presented a series of observations dealing with acute psychic reactions which are accepted by psychiatrists as spontaneous, and, therefore, unpredictable. Petersen has published detailed observations indicating that one of the major factors governing the physico-chemical status of the human organism is to be sought in the meteorologic environment. The swing in mood of the normal individual (leptosome as well as pyknic) and the swing in behavior and activity of the psychotic patient (schizophrenic as well as manic-depressive) are both influenced by the meteorologic environment. In general outline, the underlying mechanisms are relatively simple. The passage of a cold air mass is associated with vasoconstriction and increased blood pressure (peripheral, pelvic, cerebral). The relative anoxia thereby entailed is followed by a relative acidity, with lowering of the blood pressure, increase in the basal metabolic rate, etc. (COD phase). Such metabolic swings are accentuated in the later winter and spring. The more acute biochemical changes follow in the wake of a polar front, and in the susceptible individual (considering here particularly the slender, poorly buffered individual whose central nervous system may have been conditioned thus either by genetic constitution or by the environment at the time of conception) will be associated with evidence of clinical activation. This is evident in acute schizophrenic episodes which occurs after a period of vasoconstriction, when the blood pressures are lower, when the blood pH is low, and when there is every evidence of tissue stimulation (or its sequel, over-stimulation and fatigue).

On the other hand, the opposite status is associated with the onset of the acute episode (hypomania) in the manic depressive. Here it is the period of acute anoxia, coincident with a period of undue vascular spasm, that precipitates the change in the mood or in the psychotic picture. Here a relative alkalosis is dominant, smooth muscle in general is in a state of increased tone, the potassium: calcium ratio is high, the vessels are relatively impermeable, the blood sugar is higher, the tissues are in a state of relative dehydration.

In an unstable individual, major endocrine and biochemical swings may definitely affect the reaction of the central nervous system. If the central nervous system is potentially inadequate because of genetically or environmentally conditioned inadequate development, such swings may precipitate acute

thymergasic reactions in the pyknic manic-depressive, or activation of acute parergasic reactions in the leptosome schizophrenic. In the schizophrenic, the trend is toward activation in the late winter and spring; in the manic-depressive, by contrast, the activation of acute episodes comes in the summer and late autumn. This association is based on the fact that the later winter and spring reveal an accentuation of biochemical trends toward low pH, while the summer and autumn trends are toward an alkalosis in practically all individuals. Naturally, trends toward acidosis are accentuated in the slender, poorly buffered individual (more often the schizophrenic) and toward a relative alkalosis in the pyknic type (more often found in the manic-depressive group).

Dysharmony of the internal milieu of the organism is not recognized by the patient, just as the psychotic individual does not appreciate the significance of his emotional feelings, drives, and reactions.

Major chemical waves mirror the passage of atmospheric changes. Within reasonable limits, we are not conscious of them except in our minor moods and feelings, including constipation and sleep. But if tissues are not able to adjust to these repeated and finally upsetting biochemical swings, we register clinical symptoms which indicate failure of synchronization in the totality of the biologic pattern.

Generally, the ARS phase, i.e., the pressor episode, is associated with the passage of a "polar front" and is, therefore, associated most often with an acute thymergasia of the manic-depressive, while the subsequent "tropical" air mass, passing in the wake of an acute polar episode, is more often associated with the development of an acute parergasia in the schizophrenic.

We have described material from European sources to rule out any factor of personal selection and to prove that conditions which have been demonstrated for our country will be found valid for any region. Meteorobiologic correlations of this type have the advantage that, from properly dated clinical records, it is always possible to integrate at least the meteorological environment on a factual basis—a condition that is by no means attainable when less well defined environmental factors such as diet, social and economic milieu, or situational factors are considered.

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POSTERIOR-FOSSA TUMORS AND THE ELECTROENCEPHALOGRAM[1]

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INTRODUCTION

Some time ago one of us made the comment that, in our experience, disturbances of electrical potential activity primarily occipital in localization were not usual in patients with clinical symptoms referable to the posterior fossa (18).

This observation was at variance with Smith, Walter, and Laidlaw's (18) report of four cases with verified cerebellar tumors, one tumor of the third ventricle causing considerable compression of the structures of the posterior fossa and two cases without operative verification but unequivocal clinical signs of cerebellar lesions, all of whom gave delta wave localizations to the occipital and posterior parietal region on electroencephalographic examination.

Cases mentioned by other investigators have shown considerable variation of the electrical pattern recorded from patients with cerebellar tumors. Walter (22) states that, "In a few cases of cerebellar tumor a delta focus has been found on the side of the tumor by leading off from just behind the mastoid process" (p. 377).

Marinesco, Sager, and Kreindler (15), comparing bilateral records obtained with forehead-occiput or forehead-vertex-occiput leads, reported a slower frequency with increased amplitude, and a slower frequency of decreased amplitude on the side corresponding to operatively verified tumors of the cerebellar vermis on the left, and of the left cerebello-pontine angle respectively.

Of Lyman's (14) one hundred electroencephalographic records, sixteen were obtained from patients revealing, on operation, tumors of the cerebellum, cerebello-pontine angle or fourth ventricle. Seven of these showed fairly definite occipito-parietal localization of slow potentials within approximately a 1–3 per second frequency range.[3] So far as can be judged from the records, and the information concerning the tumor location supplied, there is little correlation between the apparent focus or maximum concentration of slow activity and the position of the tumor within the posterior fossa. A considerable variety of potential pattern was displayed in the remaining nine records.

Referring to the occipital delta focus described by Smith and his co-workers, Gibbs, Munro, and Wegner (10) say that, "In our experience such foci are usually lacking" (p. 281) but, so far as we are aware, no report of cerebellar cases has appeared from the Gibbs' laboratory.

In view of this confusion of opinion, the paucity of reports on the electro-

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[3] These analyses have been made by us since the atlas includes only the reproductions of the records, without interpretation.

encephalographic data obtained from patients with verified tumors of the posterior fossa appears to us to be unfortunate. If as Walter (23) puts it, "Tumors below the hemispheres cannot be localized though their indirect effects can sometimes be observed" (p. 4), it is important that the electroencephalographer become familiar with the variety and character of such effects in order that he may recognize their possible association with lesions removed from the observed location of the electrical disturbance. It is for this reason that the writers have undertaken a review of the electroencephalographic data in a series of verified posterior fossa tumors occurring among their cases.

METHODS

Material. The study is based upon the analysis of records from thirty-nine electroencephalographic examinations of twenty-three patients with verified tumors of the posterior fossa. Twenty-five of the records were obtained before operation. Twelve of the patients have died. Unfortunately adequate autopsy reports were obtained on only four cases. All of the eleven patients still living have been reexamined postoperatively.

A summary of the case material with age, operative findings, histological diagnosis, present clinical status and times of electroencephalographic examinations for each patient is given in Table I.

Recording techniques. Grass amplifiers and ink-writing oscillographs allowing simultaneous recording through at least two, and in the majority of the cases four independent channels were used throughout. Electrodes were of chlorided silver, fastened to the scalp with collodion and making electrical contact through a chloride jelly. Resistance between electrodes did not exceed 10,000 ohms.

The patient reclined on a bed in a dimly lit electrically shielded room. Changes of condition and movements were observed through a window or directly from the bed-side and noted immediately on the record.

A minimum of 14 electrode placements (7 bilaterally symmetrical positions on the 2 sides of the head) have been essentially similar for all individuals. They consisted of:

1. Frontal electrodes: 3 and ±7 centimeters from the mid-saggital line on a line joining the external auditory meati and crossing the midline at a point approximately one-quarter the glabella-inion distance.
2. Central electrodes: 3 and ±8 centimeters from the mid-sagittal line on a line joining the external auditory meati and crossing the midline just posterior to a point one-half the glabella-inion distance.
3. Occipital electrodes: within the borders of the occipital bone approximately 2½ and 4 centimeters from the mid-saggital line, the former on a level with, the latter 3½ centimeters posterior to the lambda, giving an electrode separation of 3 centimeters.
4. Mastoid electrodes: on the mastoid portion of the temporal bone posterior and slightly superior to the external auditory meatus.

Precentral, parietal, anterior and posterior temporal placements have also been used when additional information appeared to be desirable.

Routine recording methods included:

1. Bipolar: between the paired electrodes of the same region.
2. Mastoid: between the lateral member of each pair and the mastoid electrode of the same side.
3. Antero-posterior: between electrodes in different regions.
4. Midline: between the medial electrodes of the 2 sides.
5. Intermastoid: between the 2 mastoid electrodes.

Bilateral and regional comparisons with each of the above, phase reversals with electrodes in line and triangulations were also employed to determine in so far as possible the contribution of each individual electrode to the patterns obtained.

TABLE I

Case material

NAME	AGE	OPERATIVE AND NECROPSY FINDINGS	CLINICAL STATUS, 1941	E.E.G. DATES	
				Pre-op.	Post-op.
A. B.	49	10/16/41: Right cerebellar cyst with adjacent gliosis	Symptom free	10/ 7/41 10/11/41	10/27/41 12/19/41
B. B.	20	1/5 and 1/22/40: Bilateral acoustic perineurial fibroblastomata	Died 1/28/40	1/ 3/40	
B. C.	38	1/8/40: Left cerebellar metastatic carcinoma	Died 5/6/40	1/ 5/40	
S. C.	16	11/14/39: Cerebellar astrocytoma; vermis and both hemispheres L > R	Symptom free	11/ 6/39	11/15/41
L. E.	50	10/13/39: Right cerebellar metastatic papillary carcinoma	Died 12/22/39	9/14/39 9/29/39	
A. G.	55	3/7/40: Left cerebellar metastatic carcinoma	Died 5/ /40	2/24/40	
M. G.	41	11/3/41: Right cerebellar astrocytoma	Residual signs improving	10/28/41	11/22/41 1/3, 2/12/42
Y. G.	54	7/24/40: Left acoustic perineurial fibroblastoma	Slight residual symptoms	7/16/40	12/12/41
H. H.*	27	10/24/41: Right acoustic perineurial fibroblastoma	Died 10/26/41	10/23/41	
P. H.	50	5/31/40: Left cerebellar metastatic carcinoma	Died 7/17/40	5/28/40	
G. L.	51	5/21/41: Right cerebellar hemangioblastoma	Died 5/27/41	5/17/41	
H. L.	39	4/15/40: Cerebellar medulloblastoma; vermis and both hemispheres	Slight recurrent symptoms	4/ 2/40	12/11/41
J. L.	5	4/1/40: Left cerebellar abscess	Symptom free	3/28/40	1/ 5/42
B. M.	47	12/11/39: Left acoustic perineurial fibroblastoma	Slight recurrent symptoms	12/ 8/39	12/19/41
H. M.	38	9/19/38: Right cerebellar hemangioblastoma	Symptom free	9/12/38	11/24/41
R. N.*	34	11/28/38: Left acoustic perineurial fibroblastoma	Died 11/15/40	11/17/38	
R. O.	56	4/18/41: Cerebellar vermis cyst. 7/2/41: Metastatic carcinoma	Died 7/4/41	4/16/41	
H. R.	58	1/23/39: Left acoustic perineurial fibroblastoma	Slight recurrent symptoms	1/20/39	1/20/42
L. R.	39	7/18/39: Cerebellar vermis ependymoblastoma invading fourth ventricle	Spinal implantations	7/ 6/39	11/17/41
S. T.	32	5/18/39: Fourth ventricle choroid plexus papilloma	Psychopathic institution	5/18/39	6/14/39
S. V.*	10	1/29/40: Cerebellar medulloblastoma; vermis, hemispheres, fourth ventricle	Died 1/30/40	1/29/40	
A. W.	20	11/27/39: Left cerebellar tuberculoma	Died 1/18/40	11/27/39	
C. W.*	11	7/1/40: Cerebellar medulloblastoma; vermis, hemispheres, invading fourth, third and left lateral ventricles	Died 7/6/40	6/27/40	

* Cases with complete necropsy reports.

Records from normal individuals under basal conditions with the above electrode placements and recording methods show the generally accepted "normal" electroencephalographic patterns, regional and bilateral relationships.[4] The intermastoid lead gives activity which in frequency, per cent time and rhythmicity of alpha and beta potentials is intermediate between that recorded from occipital and central regions, irregularities of base-line which are more comparable to those of the frontal records and amplitudes falling within a range which varies between approximate equality with and 1½ times that of similar occipital frequencies.

RESULTS

Analysis of the records. Indications of change from normal electrical potential patterns[5] fell primarily into the following categories:

I. Slow dysrhythmias (±1–6 or 7 per second or equivalent duration) usually variable in, but sometimes displaying considerable regularity of, period. They appeared: (a) Uncomplicated by faster frequencies. (b) Underlying an essentially normal or mixed alpha and slow wave pattern. (c) Randomly distributed among more or less activity of the alpha and/or beta range.

II. Potentials fulfilling the requirements of alpha except for unusually slow (7–8 per second) or scattered (±8, 10, 14–18 per second) frequencies.

III. Groups of potentials of equal or unequal periods set off from the surrounding pattern by a rather abrupt increase of amplitude without any striking change in or uniformity of frequency.

IV. Bilateral differences in both the above and more normal activity. These included assymmetry of similar patterns allowing no adequate judgment of greater or less normality as well as more definitely lateralized indications of change from normal.

V. Unusual regional distribution of alpha in per cent time and/or amplitude relative to that recorded from the occiput.

A summary of the distribution of these disturbances in the four recording areas of the 25 preoperative records (Table II) serves to give some indication of the individual variation as well as the combinations of abnormalities observed. No record was considered to be absolutely normal and in only one case was one region alone affected. Out of the 24 possibilities changes of some character were present in 21, 22, 20 and 23 of the frontal, central, mastoid and occipital records respectively.

A grading from greatest to least abnormality and bilateral difference in the affected areas of each individual record is shown in figure 1. Except for the designation of those effects which were very slight no attempt was made to represent the absolute magnitude of the disturbance from area to area or individual

[4] For recent discussions of recording techniques and potential patterns see Davis (4), Gibbs and Gibbs (9), and Jasper (11).

[5] Only those effects appearing at a magnitude of amplitude or per cent time judged to be significantly greater than those observed in the records of normal individuals have been included in this analysis.

TABLE II

Types of abnormality found in preoperative E.E.G.'s and their representation in the four recording regions of each individual record

	TYPE OF ABNORMALITY																														TOTAL			
	Ia				Ib				Ic				Ib & c				II				III				IV				V						
	F	C	M	O	F	C	M	O	F	C	M	O	F	C	M	O	F	C	M	O	F	C	M	O	F	C	M	O	F	C	M	O	F	C	M	O
A. B. 1, 2									X	X	X	X									X	X	X		X	X	X	X			X		3	3	4	2
B. B.																												X					0	0	0	1
B. C.									X	X	X									X	X	X	X		X	X	X						3	3	3	1
S. C.	X									X					X						X	X						X						2	2	1	1
L. E. 1					X			X									X	X	X	X					X	X	X	X	X	X	X		4	3	3	3
L. E. 2	X		X			X		X										X		X					X	X	X	X		X			2	4	2	3
A. G.					X	X	X	X									X	X	X	X					X	X	X	X		X	X		3	4	4	3
M. G.									X	X	X					X					X	X	X		X	X	X	X		X	X		3	4	4	2
Y. G.																						X						X					0	2	0	1
H. H.															X	X					X	X	X		X	X	X	X					2	2	3	2
P. H.					X						X												X								X		1	0	3	0
G. L.							X	X													X	X				X		X		X	X		1	3	2	2
H. L.	X	X	X																									X					1	1	1	1
J. L.													X	X	X	X												X					1	1	1	2
B. M.									X	X	X	X									X		X	X	X	X	X	X		X			3	3	3	3
H. M.					X			X																				X					1	0	0	2
R. N.						X							X												X	X		X					2	2	0	1
R. O.	X		X											X		X									X	X							2	2	1	1
H. R.																						X				X	X	X					0	2	1	1
L. R.									X	X	X	X									X	X	X			X		X					2	3	2	2
S. T.	X					X	X																			X		X					1	2	1	1
S. V.	X		X	X		X																X			X	X	X	X					2	3	2	2
A. W.								X	X	X					X						X	X	X				X	X					2	2	3	2
C. W.					X	X	X	X																		X		X					1	2	1	2

F, frontal; C, central; M, mastoid; O, occiput.

For a description of the abnormalities represented by Roman numerals see text.

to individual. This somewhat arbitrary classification depended upon evaluation of:

1. The frequency, per cent time and amplitude of disturbances of similar character appearing in more than one area.
2. The degree of change from normal expectancy encountered in areas affected by different types of disturbance (i.e., a fair per cent time of good amplitude slow dysrhythmias being rated more abnormal than a rhythmic 7–8 per second alpha or a bilateral difference in an otherwise normal pattern).
3. The per cent time distribution of a rhythmic pattern of alpha and/or beta frequency superimposed upon slow potentials which did not themselves show any regional magnitude balance.

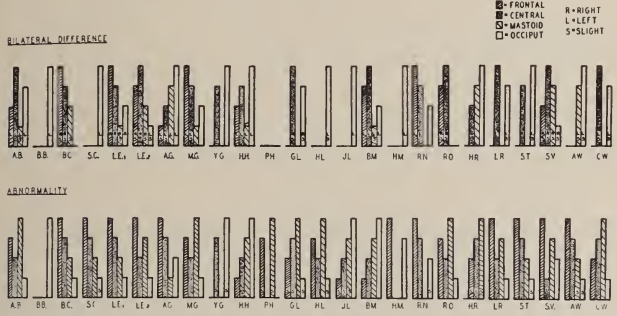

FIG. 1. Distribution of abnormality and bilateral difference in the four recording regions of the individual preoperative electroencephalograms.

Column heights represent an arbitrary four step grading from greatest (highest column) to least (lowest column) abnormality or bilateral difference for each record. They are not comparative as to the degree of disturbance from individual to individual.

S. designates that the change from normal was slight in absolute magnitude.

A blank denotes activity and general bilateral synchrony within normal limits.

L (left) and R (right) indicate the side on which the greatest abnormality was observed. Absence of such lettering shows asynchrony or dissimilarities which did not allow a definite sidedness judgment.

4. The less as against the more normal side where bilateral differences existed and the amount of such differences.

The analysis revealed maximum abnormality of the occipital area in six, the mastoid region in seven, and the frontal area in ten cases.

The variety of both pattern and distribution of abnormality suggested influence from more than one source of disturbance and made necessary a consideration of correlation with such possible complicating factors as increased intracranial pressure, state of consciousness, and supratentorial lesions, before the importance of effects produced primarily as the result of the posterior fossa tumor could be estimated.

TABLE III

Intracranial pressure, state of consciousness and clinical impression at the time of the electroencephalographic examination

NAME	CSF	PAPILLEDEMA	AIR STUDY	STATE OF CONSCIOUSNESS	CLINICAL IMPRESSION
	mm.				
A. B.	180	None	Ventricles considerably dilated	Confused	Degenerative cerebral disease
B. B.	400	Bilateral, well marked early	Not done	Normal	Neoplasm, bilateral acoustic or cerebellar, involving pons
B. C.	124	Bilateral, moderate with hemorrhages	Dilated ventricles	Normal	Neoplasm, probably frontal
S. C.		Bilateral, advanced	Slightly dilated ventricles	Normal	Neoplasm, third ventricle or posterior fossa
L. E. 1	180	Bilateral, R > L, hemorrhages on R	Ventricles not dilated	Normal	Neoplasm, cerebellar and/or right cerebral
L. E. 2	480	New hemorrhages	Moderately dilated ventricles	Lethargic	Same
A. G.	120	Blurring of disc margins L > R	Dilated ventricles*	Somewhat confused	Meningo-encephalitis
M. G.	360	Blurring of nasal margins R > L	Tremendously dilated ventricles	Normal	Vascular, inflammatory, or possibly cerebellar neoplasm
Y. G.	215	None	Not done	Normal	Neoplasm, left acoustic
H. H.	420	Bilateral, acute	Not done	Normal	Neoplasm, posterior fossa involving brain stem
P. H.	326	Blurred disc margins; fullness of veins	Dilated ventricles	Lethargic	Neoplasm, cerebellar, probably metastatic
G. L.	395	Bilateral; recent hemorrhages	Slightly dilated ventricles	Normal	Neoplasm, posterior fossa, or intraventricular
H. L.	125	None	Markedly dilated ventricles*	Normal	Questionably neoplasm, localization uncertain
J. L.	320	Bilateral	Not done	Somewhat drowsy	Left cerebellar abscess
B. M.	400	Bilateral, low grade, with hemorrhages	Not done	Normal	Neoplasm, left acoustic
H. M.	210	Slight fullness of veins	Not enlarged	Normal	Labyrinthitis or neoplasm, right acoustic

TABLE III—*Continued*

NAME	CSF	PAPILLEDEMA	AIR STUDY	STATE OF CONSCIOUSNESS	CLINICAL IMPRESSION
	mm.				
R. N.	190	Slight blurring of nasal margins	Somewhat dilated ventricles	Normal	Neoplasm, neurological localization questionable
R. O.	190	Bilateral, well marked	Dilated ventricles	Stuporous	Neoplasm, neurological localization questionable
H. R.		None	Not done	Somewhat apathetic	Neoplasm, left acoustic
L. R.	350	Bilateral, marked	Somewhat dilated ventricles	Lethargic	Serous meningitis
S. T.		Bilateral, advanced	Dilated ventricles	Normal	Neoplasm, posterior fossa
S. V.	600+	Bilateral; secondary optic atrophy	Markedly dilated ventricles	Stuporous	Neoplasm, probably posterior fossa
A. W.		Bilateral, with hemorrhages	Markedly dilated ventricles	Normal	Neoplasm, posterior fossa
C. W.	330	Fullness of veins	Slightly dilated ventricles	Stuporous	Neoplasm, posterior fossa, predominantly left

Except where noted (*) air studies were made within one week after, other measurements and estimations coincidently with, or within one to two days of the E.E.G.

CORRELATIONS WITH CLINICAL DATA

I. *Intracranial pressure and the state of consciousness.* Measurements of cerebrospinal fluid pressure, evidence of papilledema, results of air studies and estimations of the state of consciousness at the time of the electroencephalographic examination are given in Table III.

Although two of three patients with relatively little indication of increased pressure (Y. G., fig. 2, H. R.,) gave electrical activity varying from normal by only a minor degree, the third (H. L., fig. 3) presented a high amplitude slow (4–6 per second) potential pattern from all but the occipital areas. Conversely, of the five patients with cerebrospinal fluid pressures exceeding 395 mm., all of whom had papilledema, three (L. E. 2, fig. 4, H. H., fig. 5, B. M.) showed definitely abnormal records, one (G. L.) considerably less abnormality and the fifth (B. B.) the most normal record of the series.

The presence, absence or degree of papilledema likewise showed no significant correlation with the type or distribution of the electrical changes.

Air studies were obtained on only two of those patients whose electroencephalograms revealed few or no disturbances from the majority of the recording regions. G. L., with slight dilatation, showed somewhat more definite indications of abnormality than did P. H. whose ventricles were definitely dilated. Considerable ventricular dilatation (A. B., M. G., H. L., S. V., A. W.) was not associated with any specific type or distribution of electrical pattern nor with a

magnitude of disturbance necessarily greater than that recorded from other patients. Where a considerable difference between the sizes of the two ventricles was found there was no significant correlation with lateralizations of the electrical potentials.

Records from three patients who were almost completely out of contact with the environment (R. O., S. V., C. W.) gave a more diffuse and constant repre-

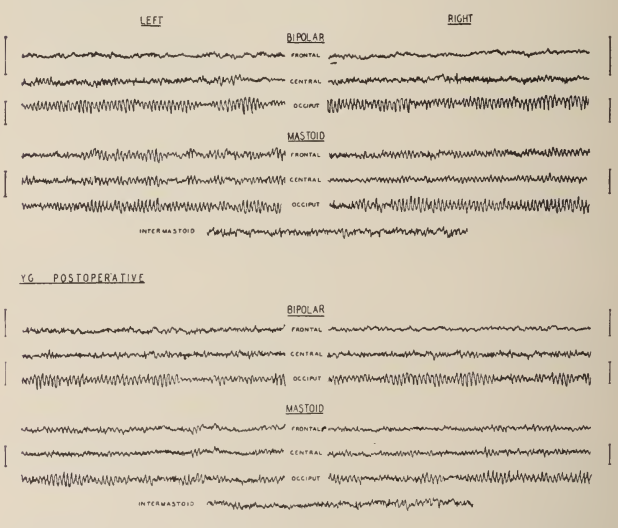

FIG. 2. Y. G., 54 year old female. Twitches, numbness, dizziness and unsteadiness beginning four to five years ago. Incoordination, nystagmus, absent left corneal reflex, left deafness. Left perineurial fibroblastoma verified by operation.

Electroencephalogram: Preoperative: Record essentially normal except for slight asynchrony bilaterally. Postoperative: One and a half years after operation. Activity similar to that previously recorded except for some decrease in the alpha amplitude from the mastoid leads.

sentation of slow (1–3 per second) activity than was obtained from the remainder of the series. In each of these cases short periods of fairly normal potentials relatively undisturbed by the slower waves were observed to be correlated with objective evidence of alertness.[6] Other individuals with higher pressures showed

[6] Removal of ventricular fluid and insertion of air through previously made frontal burr holes was carried out simultaneously with the taking of the electroencephalogram on S.V. A total of 98 cc. of fluid were removed and 80 cc. of oxygen inserted with electrical samplings made at intervals during the procedure. Unless the patient became active there was no essential change of pattern observed.

no impairment of consciousness, and there was no significant relationship between the estimated degree of alertness and the electrical pattern obtained for other than the three patients most nearly comatose.

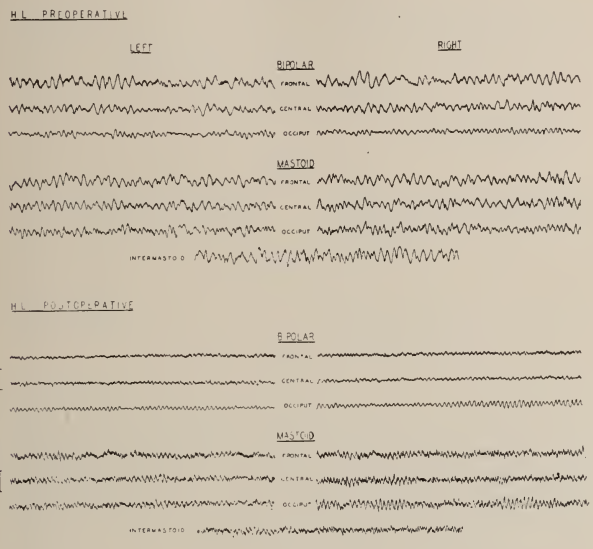

Fig. 3. H. L., 39 year old female. Headaches, weakness, unsteadiness of two months duration; tendency to fall to right. Equilibratory incoordination; increased deep reflexes and positive Oppenheim and Gordon signs on the right. No papilledema. Medulloblastoma of superior cerebellar vermis verified by operation.

Electroencephalogram: Preoperative: Note the relative normality of the occipital bipolar potentials and the bilateral distribution of the ±5–6 per second of other regions. A judgment of maximum abnormality from the region of the mastoids (see text and fig. 1) was given on the basis of a greater per cent time of disturbance from these than from the frontal regions. Except for this the pattern is essentially similar to that observed in many cases where the maximum abnormality was frontal (see text).

Postoperative: Twenty months after operation. There is some asynchrony of the occipital alpha.

These findings are in essential agreement with those of Williams (24) who stated that in his patients "There was little correlation between the pressure and its effects on the state of consciousness of the subject and on the changes seen in the electroencephalogram" (p. 334).

II. *Clinical impression.* Clinical neurological data were sufficiently indicative of the presence and location of a neoplasm to warrant operation without air

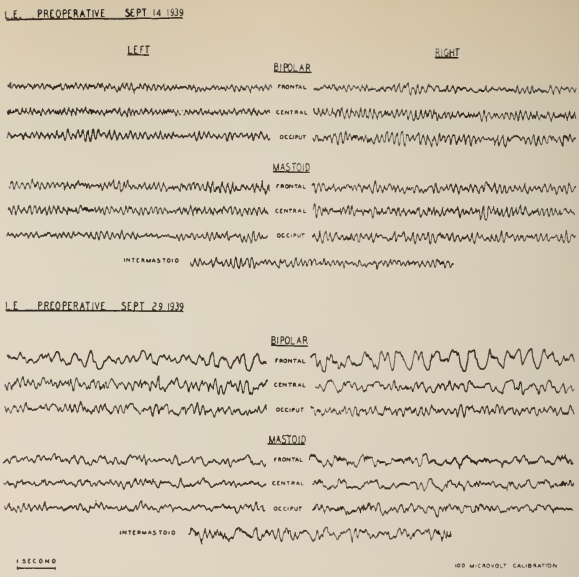

FIG. 4. L. E., 50 year old female. Onset of severe headache four to five weeks prior to admission. Vomiting, fainting spells, pain in back of neck intermittently since then. Slight incoordination right upper extremity; bilateral papilledema; slight left central facial weakness; diminished sensation ulnar side of left hand. Metastatic carcinoma of right inferior cerebellar hemisphere verified at operation.

Electroencephalogram: 11/14/39: Note the high per cent time of $\pm 7\frac{1}{2}$–8 per second from all areas. Frontal and mastoid activities on the right show slower potentials than those on he left.

t11/29/39: Note marked increase in slow potentials bilaterally and the unequal regional distribution of the effect. For change in patients condition see text.

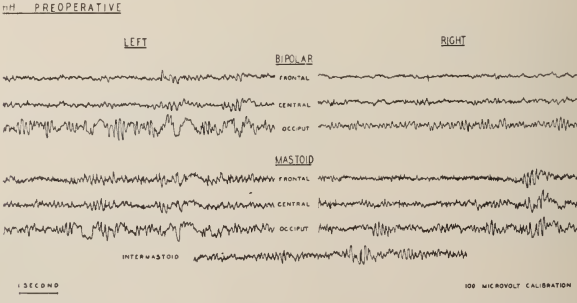

FIG. 5. H. H., 27 year old female. Headaches and unsteadiness of gait for three months followed by difficulty with vision and swallowing. Papilledema, nystagmus, absent right corneal reflex, right peripheral facial palsy, right-sided deafness. Increase of deep reflexes and positive Babinski on right. Right acoustic perineurial fibroblastoma verified at operation. Postoperative death.

Electroencephalogram: Right bipolar records essentially normal. Definite left occipital abnormality with some disturbance of both mastoids and of the left central and frontal patterns.

study in six cases. All of these gave electrical evidence of maximal disturbance posteriorly, although in the majority of instances the effect was slight (see below).

The other patients with clinical evidence strongly suggestive of a posterior fossa lesion (P. H., S. T., S. V., A. W., C. W.) had electroencephalograms which neither in type nor distribution of abnormality could be distinguished from those obtained from the twelve whose clinical signs were less definite.

III. *Possible supratentorial lesions.*

PATIENT	CLINICAL SIGNS OF SUPRATENTORIAL INVOLVEMENT	
	Preoperative	Postoperative
A. B.	Bilateral frontal	None
B. C.	Slight left central	Multiple
L. E.	Right post parietal	Increased right post parietal
A. G.	Multiple, R > L	Multiple, slightly improved
P. H.	None	Right central
H. L.	Questionable left central	None
R. N.	None	Central, L > R
L. R.	Questionable right central	Generalized seizures
C. W.	None	Autopsy shows tumor invading left lateral ventricle

Those patients whose clinical signs indicated possible supratentorial involvement distinct from symptoms referable to the posterior fossa are noted above.

In three cases (L. E., R. N., C. W.) the greatest electrical abnormality was recorded from the clinically affected side. This was of particular interest in the patient, L. E. from whom two preoperative records were obtained (fig. 4). In comparison with the first record the second, taken fifteen days later during which time clinical signs of a right post central lesion and intracranial pressure both increased while cerebellar signs remained slight, showed (a) greater abnormality from all regions; (b) least change in the occipital pattern; (c) decrease in the bilateral differences of all but the central area and; (d) a change in the sidedness indication occipitally.

Although neurological examination of A. G. suggested multiple cerebral lesions, ventriculography revealed ". . . asymmetrically dilated ventricles, the right larger than the left. There appears to be no displacement from the midline but the length of the left ventricle is distinctly shorter than the right, and appears telescoped forward suggesting a mass in the left occipital region." Electroencephalographically he showed "1) diffuse electrical irregularity with minimal effect in the right occipital area; 2) bilaterally increased amplitude of all anterior activities over the occipital; and 3) marked depression of activity in the left occipito-parieto-temporal region", and the comment was made that "The loss of amplitude in the occipito-parieto-temporal area on the left together with some evidence for greater slowness on the same side suggests a localized change in this region. The bilateral amplitude increase of the more anterior over the occipital areas, however, is usually associated either with diffuse changes or with effects produced secondarily by a subhemispheral disturbance. In what manner the

two may be related in this case, or whether they are independent effects is impossible to decide."

In the other cases there was little correlation between either diffuse or more localized clinical and electrical disturbances.

It would appear that, although cerebral disturbances considerably influence the patterns obtained, the effect which they produce may be overshadowed by changes which do not appear to be explained by their presence.

IV. *Operative findings.* A. *Electroencephalograms showing maximal disturbances occipitally* (*fig.* 1).

PATIENT	TYPE OF TUMOR	ANATOMICAL LOCATION
B. B.	Perineurial fibroblastoma	Bilateral, L > R
Y. G.	Perineurial fibroblastoma	Left
H. H.	Perineurial fibroblastoma	Right
J. L.	Cerebellar abscess	Left
B. M.	Perineurial fibroblastoma	Left
H. R.	Perineurial fibroblastoma	Left

Five of the six patients with maximal disturbances occipitally had operative findings of a similar nature, namely: perineurial fibroblastoma. The records from three of these (B. B., Y. G., H. R.) varied from the essentials of a normal pattern by virtue of an asynchrony and slight dissimilarity in the bilateral representation of activity which was itself within, or questionably without, the normal range (fig. 2). In only one case was the effect of sufficient magnitude and constancy to allow an unequivocal judgment of a less normal side (B. B.).

Indications of abnormality in the other two (B. M., H. H.) were considerably more pronounced in degree and affected both mastoid regions although limited in other areas to a single side. In B. M. the laterality of the maximum electrical disturbance was the same as that of the tumor.

H. H. was the only patient whose record showed what one might have considered to be a definite *left* occipito-parieto-temporal localization (including phase shifting in this area) had it not been for the appearance of similar disturbances from the right mastoid (fig. 5). Operation and autopsy revealed a single large encapsulated lesion in the *right* cerebello-pontine angle, lying on and depressing the pons.

The last patient in the group was a five year old child with a left cerebellar abscess from whom the appearance of random slow dysrhythmias diffusely represented was not considered to be indicative of gross abnormality even though it would have been so estimated had the individual been older. A bilateral difference in superimposed occipital alpha and the presence of well formed 1–2 per second potentials gave a sidedness localization corresponding to that of the lesion.

These six patients were the only ones with clinical localization sufficiently definite to warrant operation without air studies, as has been noted above.

B. *Electroencephalograms showing maximal disturbances frontally (fig. 1).*

PATIENT	TYPE OF TUMOR	ANATOMICAL LOCATION
B. C.	Metastatic	Left
S. C.	Astrocytoma	Bilateral, L > R
L. E.	Metastatic	Right
A. G.	Metastatic	Left
H. M.	Hemangioblastoma	Right
R. N.	Perineurial fibroblastoma	Left
L. R.	Ependymoblastoma	Mid-line
S. T.	Papilloma	Mid-line
S. V.	Medulloblastoma	Bilateral
A. W.	Tuberculoma	Left

With the exception of one eighth nerve, and one fourth ventricle tumor all the patients in this group had lesions of the cerebellum.

The outstanding features of the records were the high amplitude of the slow frontal patterns, appearing either continuously or in groups, similar activity from mastoid and/or central regions, and the rhythmic, comparatively undisturbed occipital potentials (figs. 3 and 4).

Bilateral differences tended to be slight relative to the magnitude of the total abnormality and to show no constant correlation with the location of the lesion (B. C., S. C., H. M., L. R., S. T., S. V., A. W.). More definite sidedness indications in three records (L. E. 1, A. G., R. N.) agreed with the lateralization of the tumor and, as has been noted, with clinical evidence of possible cerebral disturbances of the same side.

In this connection one is impressed by the rather definite localization of slow potentials to the left frontal region in R. N. contrasted with occipital irregularities of a minor nature and normal mastoid activity. It is possible that the cerebral disturbance in this case is wholly responsible for the major frontal abnormality and that only the occipital effects are referable to the eighth nerve tumor. Such an assumption would explain the dissimilarity between the abnormality localization in this record and the definitely posterior changes obtained in association with the five other perineurial fibroblastomata.

C. *Electroencephalograms showing maximal disturbances from the region of the mastoid electrodes.*

PATIENT	TYPE OF TUMOR	ANATOMICAL LOCATION
A. B.	Cyst with gliosis	Right
M. G.	Astrocytoma	Right
P. H.	Metastatic	Left
G. L.	Hemangioblastoma	Right
H. L.	Medulloblastoma	Bilateral
R. O.	Metastatic	Mid-line
C. W.	Ependymoblastoma	Bilateral and left lateral ventricle

The tumors found in patients of this group were all cerebellar.

In common with six (S. C., A. G., H. M., L. R., S. T., A. W.) of the ten records giving maximal disturbances in the frontal area these records showed in all cases the greatest bilateral similarity in the region of greatest abnormality.

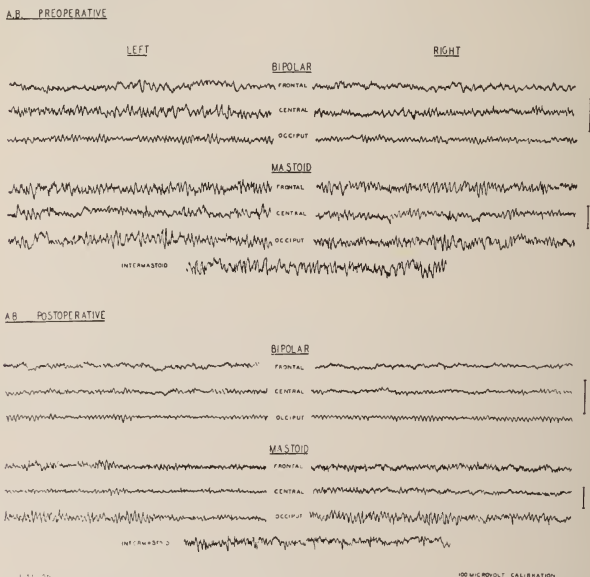

FIG. 6. A. B., 49 year old male. "Nervous breakdown", irritability, nightmares six months ago. For three months headaches, arterial hypertension; for two to three weeks unsteadiness of gait; confusion, disorientation. Aphasic, disoriented; diminished sensation on the right side, slight right central facial weakness; equivocal right positive Babinski sign. No papilledema. Right cerebellar cyst and small glial nodule removed at operation. Complete mental and physical recovery.

Electroencephalogram: Preoperative: Relatively normal occipital patterns in contrast to disturbances from other areas. Note the bilateral difference of the central regions and the bilateral similarity of the mastoid activities.

Postoperative: Two months after operation. Note the definite decrease of abnormality in comparison with the preoperative record.

Further similarities between the patterns recorded from the frontal and mastoid groups appeared in the relative normality of the occipital potentials and the high per cent time of high amplitude activity slower than alpha in frequency appearing from other areas. In the majority of cases frontal and/or central regions were affected to a degree almost equalling that of the mastoid abnormal-

ity, on both (H. L., R. O., C. W.)[7] or primarily on one (A. B., M. G.) side, while intermastoid disturbances were more constant than those recorded asynchronously from both mastoid electrodes (figs. 3 and 6).

In two instances (P. H., G. L.) the disturbances were confined largely to the regions of the mastoids and were relatively slight compared to those of other records.

There was a correspondence between the side of the lesion and that of the most abnormal activity in two cases (G. L., C. W.) including one (C. W.) in which the tumor invaded the lateral ventricle. One record (A. B., fig. 6) gave a definite lateralization to the side opposite the lesion and in general there was little localizing value in the presence or absence of sidedness of the electrical changes.

D. Summary: Omitting from consideration those cases whose records are obviously or probably influenced by supratentorial disturbances (L. E., A. G., R. N., C. W.) and those in whom the state of consciousness seemed to be of major importance (R. O., S. V., C. W.) there remain seventeen patients whose varying electrical patterns show no correlation with measurements of intracranial pressure. In general this group appeared to show:

1)A distribution of abnormality toward the occiput where the disturbance was an eighth nerve tumor (five out of five cases), and where the clinical evidence definitely indicated a posterior fossa lesion (six out of six cases).

2)A distribution of abnormality away from the occiputs in other conditions affecting the posterior fossa (eleven out of twelve cases), even though the clinical evidence strongly suggested a posterior fossa lesion.

3)A general similarity between the records with maximal abnormality localized frontally and those in which it was most obvious from the region of the mastoid electrodes.

4)A striking tendency toward bilateral equality of the greatest abnormality when this was recorded from frontal or mastoid regions (ten out of eleven cases).

5)A complete lack of correlation between the laterality of the electrical abnormality and that of the tumor.

V. *Postoperative records.* Comparison of pre- and postoperative activity showed in all cases a tendency toward: 1) Decrease in per cent time and amplitude of (a) all potentials less than 7 per second in frequency or of equivalent duration; (b) grouped activity. 2) Increase in frequency of rhythmic activity. 3) Increase in regularity of the occipital alpha.

The degree of the change was in one instance so slight that the postoperative pattern remained definitely abnormal (S. T. on whom the only reexamination was made two weeks after operation). In the majority, however, deviations from essentially normal activity were decidedly less apparent, particularly in those areas most affected preoperatively (figs. 3 and 6).

Improvement or lack of improvement in the electroencephalogram correlated in general with change in the clinical status of the patient but there was no abso-

[7] The nearly comatose condition of these patients has already been mentioned.

lute correspondence between the magnitude of the residual electrical effects and the presence or absence of neurological signs at the time of the reexamination. Of the four patients who were symptom-free (Table I) three (A. B., fig. 6, J. L., H. M.) gave almost normal patterns and one (S. C.) activity which to a slightly lesser degree differed from normal in the same direction as that recorded preoperatively. M. G., whose clinical condition improved very slowly postoperatively, gave evidence of progressive change in the three records taken.

Recurrent clinical symptoms were present in three cases (H. L., B. M., H. R.) whose electroencephalograms were considerably improved, the change represented in figure 3 being the most striking. L. R. with verified spinal metastases gave a record which was essentially normal except for a previously unobserved slow potential from the left post temporal area.

Y. G., whose preoperative activity appeared to be abnormal mainly from the point of view of greater than usual bilateral asynchrony showed little change in this factor postoperatively. There was, however, an apparent decrease in the amplitude of the alpha obtained by mastoid recording (fig. 2).

Since the removal of the major part of the tumor and the release of intracranial pressure were common to all of the operative procedures one cannot assume one rather than the other to be the major factor in the disappearance of electrical abnormality. However, were the release of pressure alone responsible one would expect the effect to be equally distributed over the cortex whereas in those patients showing definite bilateral differences the change was significantly greater on the most abnormal side. This was particularly noticeable in the case of A. B. where a left sided electrical abnormality almost completely disappeared within two months following the removal of a right cerebellar tumor (fig. 6).

DISCUSSION

At the time of the presentation of Smith, Walter, and Laidlaw's observations of occipital delta occurring with posterior fossa neoplasms (18) the suggestion was made that the discrepancies between their results and the cases which we had seen might be explained on the basis of the age groups involved. Unfortunately only one of the patients in the present report was under nine years of age (the upper limit of Smith's group,) while the records from the other two who might have been considered within a similar age range (ages ten and eleven) were complicated by a state of stupor. J. L., five years old, with a cerebellar abscess, did show a pattern and localization similar to that reported by the above authors and was the one patient of our series with a cerebellar disturbance from whom such a record was obtained.

Lyman's (14) illustrations with apparent occipito-parietal localization of 1–3 per second potentials were recorded from seven of the nine patients between one and fourteen years of age. Only two of his seven adults showed similar frequencies, one with what seems to be a right fronto-temporal, the other with a bilateral frontal localization.

There appears, therefore, to be a genuine dissimilarity between the electrical

abnormalities associated with cerebellar disturbances in children and in adults and this is further confirmed by the failure of a comparison of the symptomatology and clinical data of Smith, Walter, and Laidlaw's patients with those of our own series to show any common difference other than that of age.

In accounting for his results Smith postulated some physiological damage of the occipital cortex resulting from pressure of the tumor upward against the tentorium. Since this structure is thinner and less resistant in children than in adults it is possible that such an effect might occur more easily in the former that in the latter with a resulting preponderance of electrical changes posteriorly in the younger age group.

A similar explanation might possibly be given for the differences between the localization of abnormalities anterior to the occiputs and occipitally associated respectively with neoplasms of the cerebellum and cerebello-pontine angle in the adults of our series. Angle tumors usually lie adjacent to the tentorium and could exert direct and forceful pressure against it in contrast to the more diffuse effects produced over a wide area by the tumors of the cerebellum. Angle tumors in adults would thus tend to cause disturbances of the occipital cortex resembling those produced by cerebellar lesions in children, and of a magnitude greater than those associated with cerebellar tumors in their own age group.

An expanding lesion in the posterior fossa could conceivably produce changes in the activity of distant structures by one of two mechanisms: compression, primary or secondary, of blood vessels with resultant alteration of the vascular supply to the cortex or interference with cerebello-cortical neurone paths.

That the potentials of small, isolated groups of neurones may be made to vary over a wide range of frequencies and to show changes in form and regularity as a result of appropriate alterations of environmental conditions has been demonstrated by Libet and Gerard (13). Bailey and Bremer (1) have found moderate hypotension maintained over a period of time to produce groups of potentials of decreased frequency and increased amplitude from the cat cortex (region unspecified) in contrast to the depression encountered as the result of more drastic reductions of pressure.

Furthermore, experimental investigations involving alterations of the circulating blood and including simultaneous recording from more than one cortical area in man have definitely indicated that the cortex does not necessarily respond as a unit to alterations of the blood supply.

Low oxygen tensions are reported by Davis, Davis, and Thompson (3, 5) to give rise to the following progressive changes in the electroencephalogram: 1) slight voltage increase and 10 per second activity appearing in those records which originally had none; 2) decrease of alpha amplitude and the length of trains of alpha waves; 3) appearance of 7 and 8 per second groups of potentials at the vertex while the occipital alpha continued and 4) appearance of irregular 0.25 second and longer waves at the vertex and subsequently at the occiput alternating with alpha. Slight cyanosis and subjective changes were coincident with this last stage.

Davis, Gibbs, Davis, Jetter, and Trowbridge (6) found the ingestion of alcohol

to produce "episodes" of slow waves which became prominent when muscular tone and coordination diminished. These "episodes" were brief, more or less rhythmic, had a frequency range between four and eight cycles a second, and were most prominent from the frontal and precentral regions, least so over the occiput. Both the alpha and slower fluctuations continued to appear when the subjects became lethargic and the authors call attention to the greater similarity of the changes to those observed with the breathing of low oxygen mixtures than to those recorded in sleep.

The electrical acitivity of the anterior head regions also appears to be more appreciably altered in the direction of slow activity of increased amplitude than does that of the occipital area following the injection of metrazol (2, 7, 17).

Rubin and Freeman's (16) analysis of the potentials recorded during the induction of cyclopropane anesthesia showed the earliest onset, greatest regularity and slowest decline during recovery of 0.5–7.5 per second activity to be obtained from the frontal area while the amplitude of the potentials was at least as great as and sometimes greater than that of the waves of the premotor region. The occipital activity was the last to show the slow potentials and these never approached in amplitude or regularity those recorded anteriorly.

The absolute mechanism by which such variable factors affect the electrical activity has not been clearly elucidated and is beyond the scope of the considerations involved in the present discussion. The similarity of the activities produced in the experimental conditions to each other and to the patterns recorded from many of our patients, i.e., decreased frequency and increased amplitude from the anterior head regions with less alteration of occipital activity, would suggest that some change in the environmental conditions of the cortical cells cannot be disregarded as a possible etiological agent.

Unfortunately the responses of our so called "mastoid" activity cannot be compared directly with the experimental records. That the latter may be influenced by activity which we localize to the region of our mastoid electrode by the use of the intermastoid lead seems not unlikely since in the majority of the work quoted the data were obtained with reference electrodes on the mastoid process.

Some of our records differ specifically from those obtained under the experimental conditions cited in that the former show a definite lateralization in the magnitude of the abnormalities produced. In those instances where the sidedness was most obvious, and in which it could not be related to metastatic disease or the probable influence of a supratentorial lesion its distribution was contralateral to that of the tumor. Such effects are difficult to explain on the basis of vascular disturbances.

Walker's (21) demonstration of a change in the electrical activity from the motor cortex and surrounding areas following stimulation of the cerebellar hemispheres has shown, for the cat, an electrically excitable cerebello-cortical neurone path. Responses were mainly contralateral although ipsilateral effects were also obtained. Efferent tracts from the cerebellum with terminations in the thalamus and connecting thalamo-cortical paths to the motor cortex have been

described for primates (8, 12, 19, 20) and it is possible that some disturbance of neuronal activity adds to the anterior abnormalities observed in our records. Whether this could also explain the striking contralateral localization observed in the record from one of our patients with an angle tumor (fig. 5) is questionable.

SUMMARY

Twenty-five preoperative and fourteen postoperative records from twenty-three patients with verified posterior fossa tumors have been analyzed for the type and distribution of electrical abnormalities observed. These have been considered relative to correlations with a) indications of increased pressure; b) state of consciousness; c) clinical impression; d) possible supratentorial lesions; and e) operative findings.

The data obtained indicate that the electroencephalograms of our patients with tumors of the posterior fossa show:

1. A wide variety of type and distribution of abnormalities with effects often more apparent from anterior than from posterior head regions.
2. No correlation between pattern or distribution of disturbance and measurements of cerebrospinal fluid pressure, papilledema, or ventricular dilatation.
3. An influence ascribable to the state of consciousness only when that bordered on coma.
4. Maximal disturbances posteriorly in those cases with clinical signs unquestionably indicative of posterior fossa neoplasm.
5. An influence of probable supratentorial lesions in three cases.
6. Maximal distribution of abnormalities posteriorly in five out of six cases of angle tumor.
7. Maximal distribution of abnormalities toward the frontal or mastoid area accompanied by minimal changes occipitally in all cases of cerebellar lesion except for an abscess occurring in one child.
8. A tendency toward bilateral similarity of pattern in at least one area, most often that showing the most abnormal activity.
9. In a few instances bilateral differences with the most obvious changes contralateral to the side of the tumor.

We conclude that there is no pattern or distribution of electrical abnormality specifically indicative of posterior fossa disturbance.

We are also impressed with the possibility that the bilateral inequality of cortical changes arising in association with some posterior fossa lesions may be sufficiently suggestive of primary cortical abnormality to be so interpreted by the unwary.

We should like to express our appreciation of the assistance given us by Dr. Edith Liebling-Oestreich, Mrs. Susanne Lewyn, and Mrs. Phyllis Kuttner.

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NASO-GENITAL RELATIONSHIP

Nervous Naso-Pituitary Pathway[1]

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Since the time of Hippocrates the naso-genital relationship has often been noted but not until the end of the last century and the beginning of this century has much attention been paid to it by rhinologists and gynecologists. The first extensive and accurate observations were made by John Noland Mackenzie (1), Clinical Professor of Laryngology at The Johns Hopkins Hospital. He was interested in the relationship of the naso-genital mechanism to dysmenorrhea, the relationship of epistaxis to menstruation and pregnancy, and finally in the naso-genital mechanism, itself, as a normal process in physiology.

Mackenzie (2) called attention to the anatomical fact that the tissue covering the middle and inferior turbinated bones and a portion of the nasal septum was analogous to the erectile tissue of the penis. The tissue is made up of myriad blood vessels and blood spaces separated by fibrous connective tissue containing elastic and muscular fibres. He believed that irritations or psychical impressions caused erection of this tissue via vaso-motor nerves derived from the spheno-palatine ganglion. It is interesting to note that the laboratory experiment which is the basis for this paper demonstrates the neural connections between the nerve endings in the nose via the spheno-palatine ganglion and from the spheno-palatine ganglion ultimately to the capsule and probably to the substance of the anterior pituitary.

There is sufficient evidence to show the intimate physiological relationship between the reproductive system and the nasal erectile tissue. Frequently one can observe swelling of the erectile tissue over the turbinates and septum regularly during, just before or just after the menstrual period. Sometimes this "nasal congestion" is unilateral and at other times bilateral. It may then be the source of reflex symptoms such as coughing or sneezing and by occluding the nostrils give rise to severe headaches not infrequently mistaken for sinusitis. Females have long noted these recurring nasal congestions but not until they are asked to "date" them does the time relationship with the menstrual period become evident. Careful history taking will reveal many such cases. In a large proportion of women suffering from intranasal disease the symptoms are greatly aggravated during the menstrual period.

Recently Mortimer, Wright and Collip (3) investigated the nasal mucosa of 60 pregnant women at the Montreal General Hospital. Their findings revealed increased redness and swelling of the turbinates in 31 of the 60 cases; the redness and swelling increasing as the time of pregnancy increased. Half the women

[1] From the Laboratories of The Mount Sinai Hospital, New York City.

[2] In this article an attempt is made to sum up observations which were recorded in a series of articles published in the following journals: Arch. Otolaryng., 28: 556, 1938; Endocrinology, 23: 58, 1938; Endocrinology, 27: 463, 1940; Proc. Soc. Exper. Biol. & Med., 45: 449, 1940.

at some time during pregnancy had epistaxis. This human study was prompted by findings of similar nasal congestion at the time of menstruation in monkeys. Mackenzie reported a case of a young pregnant married woman, who, without any disease in the nose, had violent paroxysms of coughing and sneezing at times during the month which would have corresponded to the time of her menses. During the intervals between these periods the patient was free of nasal symptoms. The symptoms described above had occurred in two previous pregnancies.

Fliess (4), in 1897, reported hyperemia and swelling over certain parts of the turbinates and tuberculum of the septum. He termed these "genital spots" and by local treatment was able to alleviate certain cases of dysmenorrhea. I have been unable to corroborate the constancy of these localized swellings or genital spots described by Fliess. On the contrary I have seen these localized swellings in many different parts of all the turbinates and septum as well. He also reported intense nasal sensitivity and congestion during lactation at times corresponding to the time of menstruation. He reported several cases of abortion which he believed to be accidentally produced by nasal operations.

Brettauer (5) also reported cases of dysmenorrhea treated successfully by cocainization and cauterization of the nose. Seifert, in 1912, made a critical study of the literature and cited 300 publications on the subject. He concluded, in part, that there exists an anatomical and physiological naso-genital relationship and many indications of a direct nervous relationship but he emphasized that this nervous relationship was unknown. The work of this paper brings to light this direct nerve pathway from nasal mucosa to the pituitary. It is also interesting to note that for centuries the relation of the nasal sympathy with sexual activity has been observed. Sneezing at the beginning, during or after coitus has been reported often. One of these cases, that of a man, was observed by me.

Mortimer, Wright and Collip (6) working with female monkeys have induced redness and swelling of the nasal tissue by administering estrogenic hormones. This work by the Mortimer group was stimulated by a study of a French Canadian family in which the parents and nine children, seven female, suffered from atrophic rhinitis. X-ray examinations of the skulls showed acromegaly in all of them; four of the children displayed hypopituitarism; and two suffered from amenorrhea. It is conceivable in these cases that the pituitary function was affected through the nervous connections with the nasal mucosa rather than the pituitary affecting the nasal function.

Suggestive clinical observations corroborating some of the above phenomena stimulated a series of laboratory experiments in an effort to establish a specific naso-genital mechanism. Adult female albino rats were used and the effect of nasal treatment with silver nitrate upon the menstrual cycle noted. In this study we treated 127 animals intranasally and found a prolonged leucocytic phase in the vaginal smears of 69 (54 per cent) of these animals. Two control studies were made by using (a) sodium chloride (0.9 per cent) intranasally and (b) applying silver nitrate solutions to the buccal mucosa. Both of these gave

negative results. This study established the existence of a naso-genital relationship in which nasal stimulation elicited an ovarian response, a diestrual prolongation. On the basis of luteal ovaries and decidual reactions in traumatized uteri, this prolongation was considered pseudo-pregnancy.

Inasmuch as the action of silver nitrate depends on the concentration and volume of the applied solutions, and can range from the depression of an astringent or a cautery to the stimulation of an irritant, it was uncertain whether the nasal treatment was stimulating or depressing. Accordingly, a series of experiments was instituted treating the nasal mucosa with irritants such as oil of

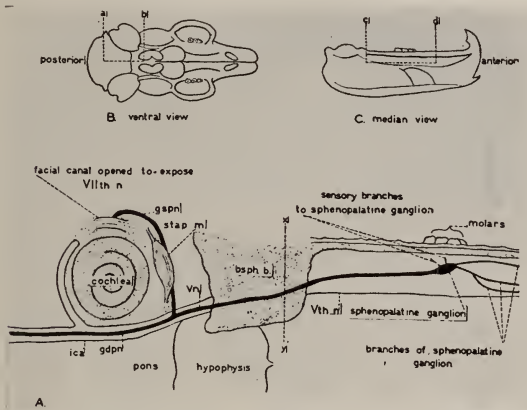

FIG. 1. A. Diagram of a dissection of a sagittally split rat's head. The portion of the diagram at the left of the sotted line xy presents a ventral view, as shown by the dotted line ab in sketch B; the portion of the diagram to the right of the line xy presents a median view, as shown by the dotted line cd in sketch C. Vth n, fifth nerve; VII n, seventh nerve; gspn, greater superficial petrosal nerve; gdpn, great deep petrosal nerve; Vn, Vidian nerve; ica: internal carotid artery; stap m, stapedius muscle; bsph b, basisphenoid bone. (From, Rosen, S., Shelesnyak, M. C. and Zacharias, L. R.: Endocrinology, 27: 464, 1940).

mustard (oleum sinapis) and by electrical shocks, and another series treating the nasal mucosa with depressants such as nupercaine. Depression was also effected by local protein precipitation with 10 per cent tannic acid and trichloracetic acid. The effect of the irritants was not that of prolonged diestrus or persistent luteal phase common to the silver nitrate effect. Nupercaine gave responses comparable to silver nitrate. In a series of 115 cases nupercaine produced the pseudo-pregnant state in 58. Traumatization of the uteri of 16 nupercaine treated animals with prolonged cycles provoked gross decidual growths in 12 cases.

The production of pseudo-pregnancy by the anesthetizing of the rat's nasal mucosa suggested the possibility of a nervous receptor factor in the naso-genital

relationship. This condition of local anesthesia was then partially reproduced by interrupting the non-olfactory nerve supply to the nasal mucosa. Since the major nasal mucosa innervation comes from branches of the spheno-palatine ganglion, it was decided that removal of the spheno-palatine ganglion would interrupt the nervous pathway of the mucosal nerves. It was found that removal of the spheno-palatine ganglion was followed by pseudo-pregnancy.

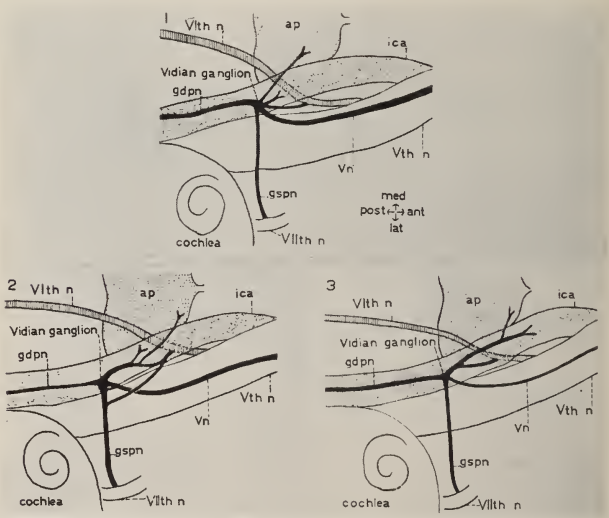

Fig. 2. Diagrams 1, 2, and 3 of dissections of the peri-hypophyseal region of rats, drawn from the ventral aspects, showing the junction of the greater superficial petrosal nerve and the great deep petrosal nerve, and the branches which arise at the point of junction. The branches are distributed to the sixth nerve, the internal carotid plexus, and the sheath of the anterior lobe of the hypophysis. Vth n, fifth nerve; VIth n, sixth nerve; VIIth n, seventh nerve; gspn, greater superficial petrosal nerve; gdpn, great deep petrosal nerve; Vn, Vidian nerve; ica, internal carotid artery; ap, anterior lobe of the hypophysis. The orientation is indicated in the lower right corner of diagram 1. (Figs. 2, 3, and 4 from: Zacharias, L. R.: J. Comp. Neurol., 74: 431–439, 1941).

In a report on this aspect of the work we (7) showed that of 150 rats with bilateral spheno-palatine extirpation 61 showed a prolonged luteal phase of the estrus cycle. The nervous factor was limited to the non-olfactory portion of the mucosal innervation, since no animals in a group of 11 showed any change in the sexual cycle after removal of the olfactory bulbs. Of the group of 61 animals with prolonged leucocyte phases, 26 were used to test for decidual cell reaction. The uterus was traumatized on the fourth, or fifth day of the prolonged leucocyte phase by passing a thin silk loop longitudinally through one horn. The animals

were autopsied on the fifth, sixth, or seventh day after the threading and the uterus was examined macroscopically for decidual tissue. All gross findings were

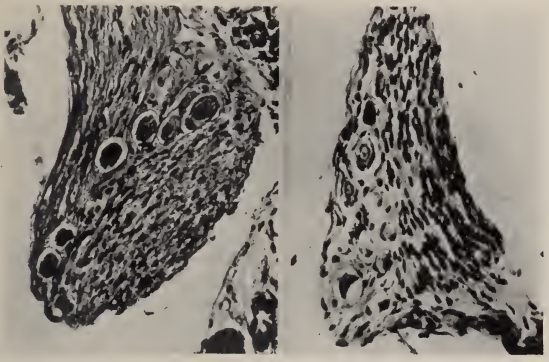

FIG. 3. Photomicrographs of two Vidian ganglia (Hematoxylin-cosin, × 400)

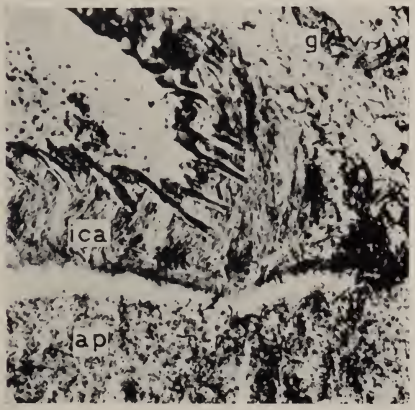

FIG. 4. Note unmyelinated fibers in the tissue of the anterior lobe of the hypophysis (ap), and also those which appear to be passing from the connective tissue around the internal carotid artery (ica) into the gland tissue (Ranson's pyridine-silver, × 250).

checked microscopically. Of these 26 animals, deciduomata were found in 17.

Long and Evans (8) demonstrated that it was impossible to produce decidual cell reactions in rats during normal four or five day cycles, and that only if the

functional life of corpora lutea is extended artificially (by sterile mating or cervical stimulation) can deciduomata be produced. Allen, states "Its formation (decidual tissue) depends directly upon the presence of functional corpora lutea." In our experiments, uterine stimulation during the prolonged leucocyte phase following extirpation of the spheno-palatine ganglion gave rise to decidual cell reaction. Decidual cell reactions in the animals in which the uteri were traumatized during prolonged diestrus indicated the presence of the functional corpora lutea of pseudo-pregnancy. Therefore, it has been demonstrated that, in the rat, interruption of the non-olfactory nasal innervation by excision of the spheno-palatine ganglion is followed by pseudo-pregnancy.

The actual relationship of the gonads to the mucosal nerves and to the spheno-palatine has been obscure. Inasmuch as the hypophysis and the nearby nerves proximal to the spheno-palatine may be in relation, a study of the anatomy of the nerve supply proximal to the spheno-palatine ganglion was undertaken.

This anatomical study of the peri-hypophyseal area was brilliantly accomplished by Zacharias (9). The dissections first performed revealed that the greater superficial petrosal nerve (para-sympathetic root of the ganglion) meets the great deep petrosal nerve (sympathetic root) at right angles to form the Vidian nerve. At this juncture a hitherto undescribed ganglion, called by Zacharias the Vidian ganglion, was seen. From this ganglion nerves emanated to three structures, the sixth nerve; the internal carotid plexus; and the capsule of the anterior lobe of the hypophysis. These were gross studies which were then corroborated histologically. The gross diagrams and histological sections are shown. The diagram of the spheno-palatine ganglion is also demonstrated (7).

It may be stated that there is a continuous nerve pathway from the Vidian ganglion to the sheath of and probably to the substance of the anterior lobe of the hypophysis. If this is true we then have an uninterrupted nervous pathway from the nasal mucosa to the anterior lobe of the hypophysis; viz, from the nasal mucosa via nasal branches to the spheno-palatine ganglion; from the spheno-palatine ganglion to the Vidian ganglion via the Vidian nerve; and from the Vidian ganglion to the sheath of the hypophysis and substance of the anterior hypophysis.

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STUDY OF CUTANEOUS HYPERALGESIA AND THE VISCERO-SENSORY REFLEX OF UTERUS AND TUBES BY MEANS OF UTEROTUBAL INSUFFLATION[1]

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In 1938 a method of studying the viscero-sensory reflex produced by distending uterus and tubes after surgical sterilization by ligation was reported in this Journal.[2] It was pointed out at that time that further study on a larger number of patients was necessary before definite conclusions could be drawn. In the present paper a report of the examination of fifteen additional cases is presented.

The mechanism of viscero-sensory reflexes is best studied experimentally by distending hollow muscular organs. Uterotubal insufflation with carbon dioxide gas has seemed to provide an ideal method of reproducing a viscero sensory reflex from uterus and tubes, the degree of distention being measurable in terms of time pressure and amount. As this procedure is carried out routinely in sterility it has incidentally afforded an admirable opportunity to observe the pain reactions produced by distending the uterus and tubes especially when partial or complete obstruction is present. The findings in cases of normal tubal patency serve as a check against the findings obtained in tubal obstruction.

It was observed repeatedly that when carbon dioxide gas passes through the uterotubal openings freely, i.e., under relatively low pressures the test is practically painless. A sense of discomfort is frequently present and localized in the suprasymphyseal region. This sense of discomfort lasts for the minute or two occupied by the insufflation and in many cases is briefly reminiscent of the unwell feeling accompanying normal menstruation.

However the sensory reaction becomes increased when the carbon dioxide gas meets with insuperable obstruction at the uterine ends of the tubes or at any point beyond the cornua. When bilateral obstruction at the cornua is encountered, the sense of discomfort felt by the patient overlying the uterus increases as a rule to pain reaction which lasts as long as the intrauterine pressure is maintained, the latter in the average case varying between 120 and 200 mm. Hg. The maximum pressure employed during uterotubal insufflation is in all cases 200 mm. Hg. In many instances this top pressure is maintained for a minute or fraction longer in order to overcome a possible spasm.

When the tubes are obstructed at points beyond the uterine ends they become distended proximal to these points and thus give rise to pain reactions with different distributions which correspond to the length of the tubal portion subjected to pressure. The pain in such instances radiates away from the midline for varying distances toward the flanks. By comparing the distribution of the

[1] From the Gynecological Service of The Mount Sinai Hospital, New York City.

[2] Rubin, I. C.: Study of pelvic pain and Head's zones reproduced by artificial distention of ligated Fallopian tubes. J. Mt. Sinai Hosp., 5: 240, 1938.

pain with the actual location of the tubal obstruction as found by laparotomy and by hysterosalpingography, it has been found possible to correlate the pain reaction with the site of obstruction and thus arrive at diagnostic data which have enabled us to dispense with both laparotomy and radiopaque solutions for the specific purpose of determining the site of tubal obstruction.

In the present study we have endeavored to map out areas of cutaneous hyperalgesia on the abdomen that accompany the pain reactions from the uterus and the tubes which are distended by uterotubal insufflation in cases where the Fallopian tubes are completely obstructed. A few cases with normal tubal patency served for comparison. In view of the rather generally confused interpretation of Head's zones, we considered it desirable to study only the distribution of cutaneous hyperalgesia attending the test for tubal patency. Our observations were focused upon the maximal points of cutaneous tenderness which Head referred to in his original contribution and not to complete bands which were supposed to involve cord segments reflecting pain emanating from diseased viscera.

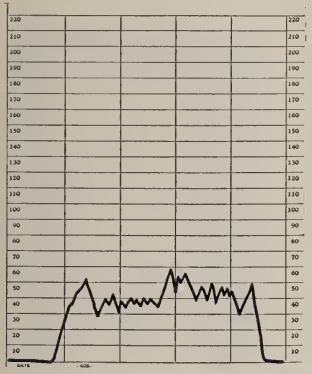
In connection with our study, Labate's report upon cutaneous hyperalgesia in relation to acute salpingitis is of special interest. Labate found that 77.3 per cent of his series of acute salpingitis showed the presence of skin hyperesthesia. Patients having the initial attack of acute salpingitis consistently showed skin hyperesthesia. The topographical zones of hyperesthesia extended from the level of the umbilicus to Poupart's ligament. Labate concluded that skin hyperesthesia occurring over the maximal areas is characteristic of acute salpingitis but must not be relied on solely in making the diagnosis.

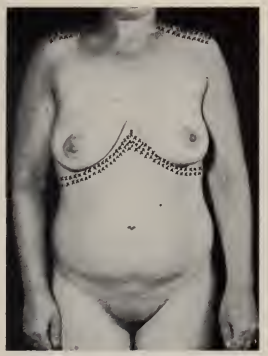
The advantage of uterotubal insufflation to determine cutaneous hyperalgesia lies in the fact that the organs involved are readily accessible to physical examination. It can be used in patients with normal Fallopian tubes and in those with varying degrees of tubal stricture or complete closure. Our present report is based upon the study of fifteen cases, five of which were demonstrated by uterotubal insufflation to have normal patency; four cases with bilateral cornual obstruction and six cases showing bilateral obstruction at the fimbria. The results were uniformly typical for each of these three groups.

The investigation was carried out in the following manner.[3] Each patient was carefully tested for normal skin sensitivity over the lower abdomen and thighs by means of pin-prick and scratch tests. The uterus and tubes were then insufflated with carbon dioxide gas delivered at a rate of 60 cc. per minute. The manometric pressure exerted within the uterus and tubes were recorded on the kymographic drum of the Rubin insufflation apparatus. The patients were instructed to indicate the moment pain was experienced when the test for cutaneous hyperesthesia immediately followed. After the insufflation the patient stood up whereupon she may have complained of epigastric discomfort or shoulder pains or both in case the Fallopian tubes were normally or partially patent. These areas were also tested for skin sensitiveness. Epigastric dis-

[3] We are indebted to Dr. Morris B. Bender for his help in the neurological technique.

comfort was due to accumulation of carbon dioxide under the diaphragm. The area of cutaneous hyperesthesia was plotted on suitable charts. The degree of tubal permeability and of the site of obstruction were correlated with the distribution of cutaneous hyperalgesia. Each case was later checked by hysterosalpingography or laparotomy.





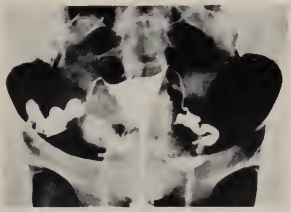


FIG. 1. Case A. O. Uterotubal insufflation graph and hysterosalpingogram reveal normal tubal patency. Note spill of viscorayopake in the pelvis, absence of hypogastric pain and hyperesthesia. On assuming an erect position the accumulation of carbon dioxide under the diaphragm produces subcostal and shoulder pain and hyperesthesia.

FIVE CASES OF NORMAL TUBAL PATENCY

Two of the patients with normally patent Fallopian tubes complained of pelvic discomfort just above the symphysis. Skin tests revealed suprapubic hyperesthesia. In three cases no pelvic discomfort was present during the insufflation and skin hyperalgesia was also absent. In none of the five cases was there any pain radiating to the right or left lower quadrants and no hyperesthesia was present over the corresponding skin areas. Suprapubic discomfort and suprapubic hyperesthesia in this group are both produced by moderate distention of

the uterus itself. The pressure required to produce patency of the uterotubal sphincter varies with each patient and in the same patient during different tests. These different pressures and the individual sensitivity to pain explain the presence or absence in normal cases of uterine discomfort and of suprapubic cutaneous hyperalgesia.

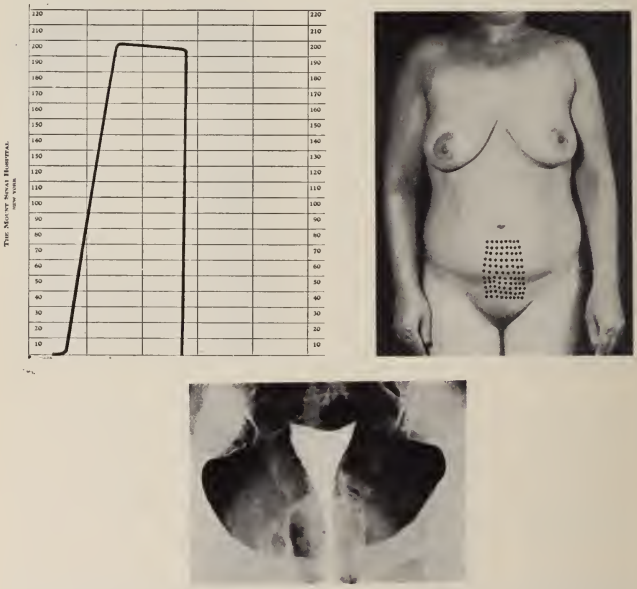


Fig. 2. Case R. B. Uterotubal insufflation showing bilateral tubal obstruction accompanied by suprapubic pain and hyperesthesia indicate bilateral interstitial tubal obstruction. Hysterosalpingogram confirms these findings.

In the presence of permeable tubes practically all patients tested by uterotubal insufflation experience after sitting up unilateral or bilateral shoulder pain; a certain number complain of subcostal discomfort. In the five normal patency cases cutaneous hyperesthesia could be demonstrated along the subcostal margins and epigastrium because considerably more carbon dioxide gas was introduced into the peritoneal cavity than is necessary for the ordinary diagnostic tubal patency test and for the same reason the shoulder pains and coincident hyperalgesia were increased. The cutaneous hyperesthesia was distributed over areas supplied by the sixth, seventh, eighth and ninth thoracic and third, fourth and fifth cervical nerves (fig. 1).

FOUR CASES OF BILATERAL INTERSTITIAL TUBAL CLOSURE

As the pressure necessary to demonstrate bilateral tubal obstruction produces marked distention of the uterus it is accompanied by pain in the lower central area of the abdomen. With the onset of pain a typical area of cutaneous hyperesthesia could be mapped out extending from the symphysis to almost the level of the umbilicus. This area extended for a distance of 2 cm. or more to either side of the midline (fig. 2).

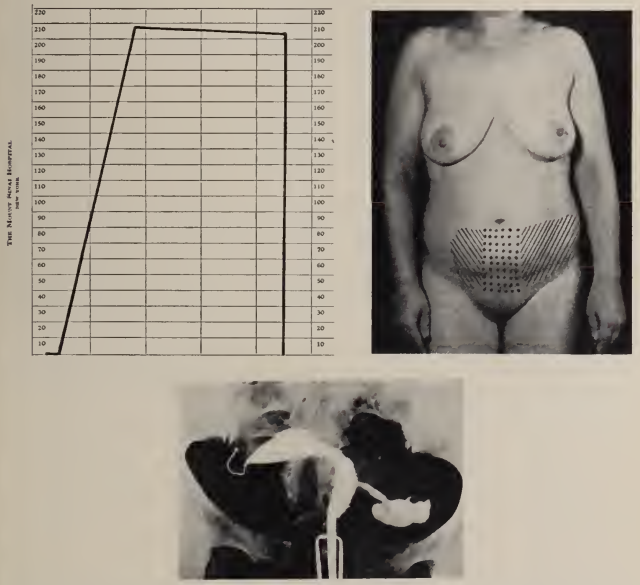


FIG. 3. Case B. Y. Uterotubal insufflation graph of nonpatency associated with suprapubic and bilateral lower quadrant pain and hyperesthesia indicate asymmetrical bilateral tubal closure beyond the interstitial portion. Hysterosalpingogram confirms the findings. Note the unequal distribution of hyperesthesia which corresponds to the difference in location of tubal obstruction.

SIX CASES OF BILATERAL FIMBRIAL TUBAL CLOSURES

These patients first experienced uterine discomfort with midline hyperesthesia. This was followed by pain radiating laterally into the lower quadrants. The onset of pain on either side was not simultaneous but cutaneous hyperesthesia was present as soon as the patient pointed to the site of pain. The area of hyperesthesia extended from Poupart's ligament to the level of the umbilicus and as far laterally as the anterior superior spine. Shortly following the cessa-

tion of the tubal distention the pain subsided and hyperesthesia disappeared. The areas of hyperesthesia coincided with those found by Labate and involved the skin supplied by the eleventh thoracic to the first lumbar nerves (fig. 3).

In the presence of permeable tubal strictures, high pressures are usually necessary to produce patency and the insufflation graph shows a paraboloid curve with slow escape of gas through the narrowed point in the tubal lumen. In these cases intratubal pressure is usually high enough to produce pain analogous to that manifested in total obstruction. We have not had occasion in our study to test for hyperesthesia in such cases, but clinically they are easily differentiated from the former by the paraboloid type of kymographic curve and the presence of subphrenic pneumoperitoneum and shoulder pains which are entirely absent in total tubal occlusion.

CONCLUSIONS

A method of studying viscero-sensory reflexes of the uterus and Fallopian tubes by uterotubal insufflation as first suggested in 1938 has been further applied in fifteen additional cases.

Definite areas of cutaneous hyperesthesia have been found to be associated and to depend upon the site of tubal obstruction and the length of the distended portion of the tubal lumen.

The areas of hyperesthesia have been found in general to correspond to the distribution of pain produced by uterotubal distention and disappear with the cessation of pain.

The characteristic patterns of skin hyperesthesia associated with obstructed tubes lend additional support to the value of pain distribution in the diagnosis of the site of tubal obstruction during uterotubal insufflation.

HYDROCEPHALUS

Analysis of Ninety-eight Cases

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[*St. Louis, Mo.*]

The treatment of hydrocephalus in infants has been a problem that has occupied the attention of neurological surgeons for a long time. Even before the advent of neurological surgery, sporadic attempts were made to treat the disease. So far, it has not been a very encouraging field and some neurosurgeons take the attitude that these cases constitute such a discouraging group that they refuse to touch them. Obviously, only if the disease is a hopeless one would such an attitude be justified. There are so many diseases that can be helped or cured today, that at one time were considered equally hopeless, that the fact that our results at present are still not very encouraging is no reason for not continuing to try to solve the problem.

It has seemed desirable, therefore, to review our experience with 98 hydrocephalics treated between 1915 and 1940. As far as we know, this is one of the largest series of hydrocephalics treated in one service and since all the children were under the same regimen the results, we believe, may be of interest and of some value. Of the 98 cases, all but 8 were operated upon.

We have seen a number of other cases of hydrocephalus during this period that were not sent into the hospital and are not included in this series. These were cases in whom the head was so very large that they were considered hopeless and we felt that the cortex had been compressed to such an extent that even if the process were arrested they could never be normal mentally. We have refused treatment more frequently in recent years for this reason as our experience has taught us that such cases cannot be helped.

There have been hydrocephalics in the Children's Hospital that were not on our service and during the life time of Dr. McKim Marriott (1) there were numerous cases that he treated with Diuretin. None of these is included in this study.

All our cases except 14 were under one year of age. We have included in this study all cases of communicating and obstructive hydrocephalus with the exception of those cases of obstructive hydrocephalus due to brain tumor. These constitute an entirely different problem and are, therefore, not considered here.

The term "communicating hydrocephalus" we apply to cases of internal hydrocephalus in which there is a free communication between the ventricles and the spinal subarachnoid space. The term "obstructive hydrocephalus" we apply to those cases in which there is no free communication between the ventricles and the spinal subarachnoid space. The obstruction may be in the aque-

[1] I have had the assistance of Dr. Leopold Hofstatter (a Fellow in Neurosurgery) in looking up these records.

duct of Sylvius, in the posterior fossa where the foramen of Magendie and the foramina of Luschka may be occluded or there may be an obliteration of the subarachnoid space about the pons.

METHODS OF DIFFERENTIATING TYPES OF HYDROCEPHALUS

Between 1915 and 1921 we made use of the method described by Blackfan and Dandy (2) of injecting a special preparation of phenosulphonapthalein into the ventricle to determine by the rate of appearance of the dye in the cerebrospinal fluid and its rate of secretion in the urine what type of hydrocephalus existed. We found, however, that the dye frequently caused high fever and so much reaction that we gave up that method and for the past twenty years have used the double puncture method. This consists in putting one spinal needle into the ventricle and another into the spinal canal and connecting each needle with a calibrated tube. If the patient has a communicating hydrocephalus, the fluid rises to the same height in each tube. Then, when the table on which the patient is lying is tilted so that the head is higher than the feet, the fluid in the ventricular manometer falls and the fluid in the spinal manometer rises an equal amount. When the patient's position is reversed, the fluid falls in the spinal manometer and rises an equal amount in the ventricular manometer. If the patient, on the other hand, has an obstructive hydrocephalus, the fluid in the two manometers will be a different height and raising or lowering the patient's head does not influence the rise or fall of the fluid. If the infant is not quiet during the examination and cries, the results may be difficult to interpret. In such a case we nowadays always anesthetize the child. The crying of the baby undoubtedly explains the wrong diagnosis in Case 65 and the difficulty we had in a few other cases.

This test does not enable one to identify cases of defective absorption but we have felt that this is not an independent type of hydrocephalus but that defective absorption may be present in both the communicating and obstructive types. If the rate of production of cerebrospinal fluid can be adequately reduced, the hydrocephalus ceases to progress, but if it cannot be controlled, no treatment will help. Cases 39, 51, 61, 74, 76, 78, 85 illustrate this situation. In these cases various procedures were undertaken. All but two of the cases had obstructive hydrocephalus and after the obstruction had been relieved the head continued to enlarge; therefore an attempt was made to reduce the rate of secretion of the fluid but even this did not help as the absorption mechanism was evidently inadequate. Only in Case 74 was this problem solved.

In all the cases in this series, we were dealing with cases of internal hydrocephalus in which the lateral ventricles were dilated and if we were dealing with an obstructive hydrocephalus the third ventricle and often the fourth ventricle was also dilated. In our experience external hydrocephalus, in which the fluid lies outside of the cortex in the subarachnoid space, is an extremely rare condition and in this entire series we have seen but one instance, Case 42. Of course, after doing a third ventriculostomy, one produces artificially an external hydrocephalus.

CAUSE OF HYDROCEPHALUS

In the communicating type of hydrocephalus we believe the underlying cause of the disease is due to hypersecretion of the cerebrospinal fluid with or without a defect in the absorption mechanism, but, even if the primary trouble is due to hypersecretion, when the hydrocephalus has become very large the pressure alone may interfere with the absorption of the cerebrospinal fluid and for that reason any treatment should be instituted as early as possible, for once absorption has become interfered with it is doubtful whether any treatment is very effective.

Our treatment of the communicating type is, therefore, directed towards reducing the source from which the fluid is secreted—the choroid plexus. We have applied the same principle of treatment that the general surgeon employs in treating hyperthyroidism, removing some of the secreting gland. This suggestion was first made by Dandy. Sometimes, as will be seen from the table, the removal of one choroid plexus has slowed up the production of cerebrospinal fluid enough to keep the head from enlarging, as in Cases 59, 60, 63, 86, 93 and 95. A balance had been reached between the secretion and absorption of fluid in these cases. For that reason, our usual procedure has been to destroy the choroid plexus on one side only and to destroy it in the opposite ventricle only if we find the head is still enlarging. In some cases the bilateral removal of the choroid plexus has not stopped the enlargement of the head and in a few cases we have then resorted to an uretero-arachnoid anastomosis.

OBSTRUCTIVE HYDROCEPHALUS

In this type, as the name implies, there is some obstruction to the flow of cerebrospinal fluid. In the majority of cases in our experience the obstruction is in the posterior fossa in the region of the cisternal magna and is inflammatory in nature, the foramina of Luschka and Magendie having become closed. In a few cases the obstruction is due to a congenital closure of the aqueduct of Sylvius and occasionally due to obliteration of the subarachnoid space around the pons. The only type of obstructive hydrocephalus that lends itself to successful treatment is that in which the obstruction is due to closure of the foramina of Luschka and Magendie. We have attempted several times to make a new aqueduct of Sylvius but have always failed. If one does succeed in making an opening in the proper region of the pons, such an opening will invariably close.

OPERATIVE TREATMENT

Up to 1929 we excised the choroid plexus as described by Dandy. While at times this was a simple procedure when the plexus had a small base, we found that there were many plexuses that were sessile and had an extensive blood supply from vessels coming from the surface of the thalamus, sometimes as many as twenty. This made the procedure a difficult one, for if one single vessel was not properly clipped the ensuing bleeding was disastrous and often resulted in a fatality. Therefore, in 1929 we began to destroy the plexus by electro-coagulation, leaving the shriveled plexus in the ventricle where it does no harm. In order to do this, it is necessary to remove the cerebrospinal fluid from the ven-

tricle and then coagulate the plexus. In doing this, it is important not to grasp the plexus with any instrument but merely to touch it, for if the plexus is grasped the coagulated plexus adheres to the forceps and in attempting to remove the forceps bleeding may be started. Bleeding into the ventricle is the one great danger in this operation. In the first place, these infants cannot stand the loss of blood and, in the second place, the presence of blood in the ventricle irritates the ependymal lining of the ventricle.

In the earlier cases we removed the ventricular fluid and put it back again but we frequently had a very marked temperature reaction and therefore filled up the cavity with Ringer's solution, but these cases also often had a marked temperature reaction. In 1932 Dr. Hartmann came to our rescue and devised an artificial cerebrospinal fluid which contained all the inorganic salts found in cerebrospinal fluid and which has the proper chemical reaction. In order to have the proper reaction, the fluid is made up in two solutions which are warmed and mixed just before using, so that they have the proper acidity. The following is the formula which we have come to speak of as Hartmann's artificial cerebrospinal solution:

The composition and preparation of Hartmann's artificial spinal fluid to replace lost ventricular fluid during the operation for hydrocephalus. At the time of injection into the ventricles, this solution closely resembles normal cerebrospinal fluid as far as content of sodium, potassium, calcium, magnesium, chloride, bicarbonate and pH is concerned. Because of its bicarbonate content, the solution has to be prepared in two parts, which, after sterilization by autoclaving and proper dilution, are mixed in equal amounts just before using.

Solution #1

(Concentrated)

	grams
$NaCl$	300.0
KCl	19.0
$CaCl_2 \cdot 2H_2O$	10.0
$MgCl_2 \cdot 6H_2O$	20.0

Fresh distilled water to 1 liter (1000 cc.)

Filter (preferably through a glass disc filter to exclude filter paper fibers). Autoclave at 15 pounds for 30 minutes. This is the concentrated Solution #1, which should keep in Pyrex glass indefinitely.

To prepare for mixing with Solution #2, measure accurately 10 cc. (with a sterile pipette, so as not to contaminate the stock solution) and make to 250 cc. with freshly distilled water. (It is convenient to do this in a 250 cc. volumetric flask. Make up to the mark, and then withdraw 10 cc. with the same pipette, leaving 240 cc.). Place this amount in a Pyrex glass flask or bottle of 500 cc. capacity, mix, and re-sterilize by autoclaving at 15 pounds for 30 minutes. Stopper with sterile (autoclaved) cork or rubber stopper. It is usually convenient to prepare about six of such bottles of 240 cc. each of Solution #1. This solution may be re-sterilized at any time, if thought advisable.

Solution #2

Na_2CO_3 (anhydrous) ..... 5.00 (exactly) grams

Add a few mgs. dry phenol red (phenolsulphonphthalein) and make to 1 liter (1000 cc.) with freshly distilled water. Filter free of any suspended particles. Measure 240 cc. into

Pyrex glass flask or bottle of 500 cc. capacity and sterilize by autoclaving at 15 pounds for 30 minutes. Stopper with sterilized (autoclaved) cork. In this condition the solution may be resterilized at any time, if thought advisable.

Just before using, add *exactly* 1 cc. (with an accurate sterile pipette) of concentrated HCl (36 per cent) to 240 cc. of Solution #2, and mix by rotating flask or bottle. The Na_2CO_3 should now be converted into $NaHCO_3 + NaCl$, and the color should change from red to an orange shade. (If such a change does not occur, a drop more of the acid should be added.) *At this stage the solution can no longer be re-sterilized.*

Pour equal parts of Solution #2 (after the addition of the HCl) into Solution #1, and mix by rotating flask. This final mixture has now the composition of normal cerebrospinal fluid, and is now ready for injection into the ventricles.

Since we have used this solution, our patients have ceased to have the stormy postoperative course they frequently had when we replaced the patient's own cerebrospinal fluid or when we used Ringer's solution. Just why the patient's own cerebrospinal fluid should have been so irritating was never clear unless it was due to the Ringer's solution we added, for we always lost some cerebrospinal fluid.

It has been claimed by some surgeons that emptying these large ventricles causes the patient to go into collapse or shock. That has not been our experience and we have therefore continued the method as we perfected it over twenty years ago. We have not made use of the instruments devised more recently by Putnam (3) and Scarff (4) for we feel we can destroy much more of the plexus by our open method for we coagulate not only the portion that lies in the body of the ventricle but also the portion that extends into the temporal horn. Secondly, if any bleeding should occur, we can control it much more readily by the open method.

Our technique is as follows: A small horse-shoe-shaped flap is made in the temporal region just above the ear (figs. 1 and 2). A small bone flap is turned down and then a dural flap is made with the base above the ear. A ventricle puncture is then done through the first or second temporal convolution, both to reduce pressure and to determine the thickness of the cortex. This is a very important point for before incising the cortex two ribbon retractors are bent as seen in Figure 2 so that the cortex, as soon as it has been incised, can be held up to the dura while the ventricle is being emptied. If this is not done, what may otherwise be a simple procedure can be very complicated and troublesome. An incision about 2 cm. in length is made into the cortex with the electric knife and two long strips of cottonoid are slipped into the ventricle to cover the cortex which is being held up by the ribbon retractors. Then the cerebrospinal fluid is sucked out of the ventricle and the choroid plexus is coagulated, using a slow coagulating current. Rapid coagulation must be avoided as this may make the plexus adhere to the forceps and will tend to char the plexus which we try to avoid. As soon as the plexus has been coagulated, the cavity is filled completely with Hartmann's solution. The dura is closed with silk, the bone flap is replaced and the scalp is closed with two layers of silk sutures, one in the galea and one in the skin.

We have performed the operation of choroidoplexectomy 62 times in these 98 patients, 55 times in cases of communicating hydrocephalus and 7 times in cases

of obstructive hydrocephalus. In 7 cases we have done a bilateral removal of the choroid plexus at one sitting. This has been done only when the septum

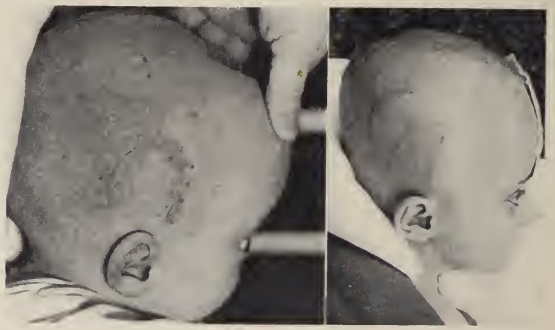

FIG. 1. Shows the type of skin flap that is used for exposing the choroid plexus

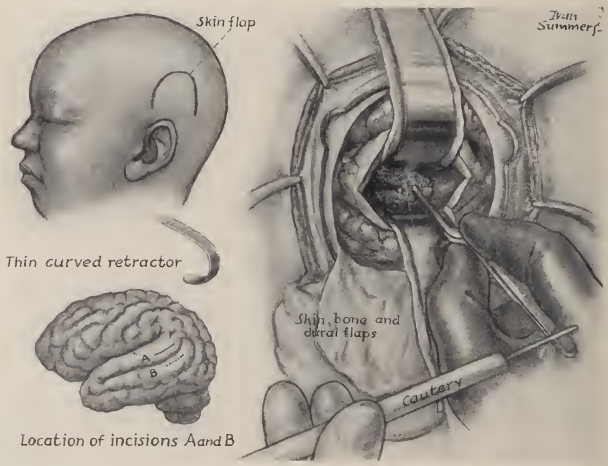

FIG. 2. Shows the exposure of the choroid plexus and the location of the incision that is ordinarily employed.

between the two lateral ventricles had a large defect in it so that it was possible to reach the plexus on the opposite side without any added manipulation but we do not recommend the procedure as it is more formidable and prolongs the oper-

ation somewhat. When this is done, both ventricles must be emptied of cerebrospinal fluid and especially long instruments must be used to reach the plexus on the opposite side. In two of the seven cases in which this procedure was carried out, Cases 45 and 87, the operation was successful.

Our policy has been to attack the choroid plexus, the source of the cerebrospinal fluid, in all cases of communicating hydrocephalus (Case 64 was the only instance in which we did not follow this rule). In the obstructive cases we first tried to relieve the obstruction; if after relieving the obstruction, as evidenced by the free flow of cerebrospinal fluid on lumbar puncture, the head still increased in size, we tried to reduce the production of fluid by removing the choroid plexus. This procedure is of doubtful value, probably because in such cases the absorptive mechanism has been so seriously impaired that reducing the production of cerebrospinal fluid by removing the plexuses in the lateral ventricles is not sufficient. It should, however, be tried unless one wishes to inject dye at this point to determine the rate of absorption. If absorption is markedly interfered with, the only procedure left is uretero-arachnoid anastomosis. We have tried third ventriculostomy a number of times for this situation, but in our experience the procedure has been of no value and we have practically discarded it.

We have done an uretero-arachnoid anastomosis in a few cases. This operation was first described by Heile (5) and consists in removing one kidney and implanting the pelvic ureter into the spinal canal and draining the cerebrospinal fluid into the bladder. It is technically not a difficult procedure but there are two points that may cause a failure. First of all, there is danger of a kink in the ureter where it crosses the bony spinal canal, and secondly, there is great danger of an ascending infection from the bladder, causing meningitis. With care the first of these can be avoided, but the second is beyond the surgeon's control.

RESULTS

It has been extremely difficult to report results accurately in a series of cases covering so many years. A certain number of cases have been lost sight of after varying periods of time. Only a limited number of cases have been followed for years and this is greatly to be regretted since one of the important points to be determined is not only whether the hydrocephalus has been arrested but also what the patient's mentality is as he has grown up. Since 1930 we have been following our cases continuously as will be noticed from table 1 (fig. 3).

We have recorded all deaths irrespective of when they occurred after operation.

In table 2, in the cases of communicating hydrocephalus, we have recorded 22 recoveries and 27 deaths. Of these deaths, 6 occurred from other causes from 1 to 2 years after operation and the hydrocephalus had been arrested. Thus, this table might very properly read 28 recoveries and 21 deaths.

It was surprising to us that our results have been definitely better in the communicating hydrocephalus cases than in the obstructive cases. This, however, we believe is readily explained by the fact that in the obstructive cases, which are usually due to some type of inflammatory process, the condition is very likely to recur; while, if the rate of secretion of cerebrospinal fluid can be slowed up in

TABLE 1

CASE NO.	HOSPITAL NUMBER	AGE	SEX	DYE INJECTED	TYPE OF HYDROCEPHALUS	TESTS	TREATMENT USED	HARTMANN'S SOLUTION	RESULTS	COMMENT
1 1915	9504	2 mos.	M	1 cc. phenolsulphonphthalein intraventricular	Obstructive (probably)		Corpus callosum puncture		Satisfactory	Dye reinjected 3 months later. Probably an obstructive hydrocephalus or tumor; today would use air
2 1915	9716	4 mos.	M	Phenolsulphonphthalein 1 cc. intramuscular 30 per cent in 1 hour. 1 cc. intraventricular, only 10 per cent recovered in urine in 6 hours	Communicating. Hydrocephalus became stationary, fontanelles closed		Cerebellar drainage 2 months later. No operation			Marked temperature elevation after injection of dye for 2 weeks
3 1915	C-8891	7 mos.	F	Phenolsulphonphthalein intraventricular. No dye recovered on spinal tap at end of 18 minutes	Obstructive, secondary to closure cerebral meningocele		Choroidoplexectomy attempted, without success		No improvement	
4 1916	10887	6 mos.	F	Phenolsulphonphthalein subcutaneously, 43 per cent recovered in urine in 2 hours. Phenolsulphonphthalein intraventricular, excreted 9 per cent in urine in 36 hours In spinal canal 12 per cent in 36 hours	Obstructive		Cerebellar operation. Opening of cyst		Died 12 days after operation (bronchopneumonia)	Marked upset by injection of dye
5 1917	381	15 mos.	F	First seen at 6 months, then phenolsulphonphthalein intraventricular; none appeared after 24 hours in spinal canal. Repeated 3 times in course of 9 months, always through right ventricle	Obstructive		Choroid plexus excision, right		Died 6 days after operation suddenly; no fever; wound healed	Pyocephalus of left ventricle developing at site of forceps injury at birth
6 1919	12826	2½ yrs.	F	Phenolsulphonphthalein intraventricular, appeared slowly in spinal canal	Obstructive		Ventriculogram, 250 cc. of air. Cerebellar opening of cisterna magna		Discharged much improved	

7 1919	13813	2½ yrs.	F	Phenolsulphonphthalein intraventricular; dye appeared promptly in spinal canal, 39 per cent in 76 hours. Injected dye spinal canal, 63 per cent in 20 hours. Defective absorption	Communicating		Cerebellar craniotomy, opening basal cisterna		Improvement	
8 1920	16876 M	5 mos.	M		Obstructive, following meningitis		Suboccipital craniotomy		One year later, doing well. Hydrocephalus apparently arrested	
9 1920	930	9 yrs.	M		Obstructive		Cerebellar decompression		Uneventful recovery	Pathology not explained
10 1920	15832	4 mos.	M	Intraventricular injection of antimeningococcus serum—cured. Phenolsulphonphthalein test 2 months later—dye in spinal canal in traces	Obstructive		Cerebellar craniotomy with opening of large obstructive cyst		Wound infection. Died of meningitis ten days after operation	
11 1921	18203 M	1 mo.	F		Communicating, following closure of spina bifida		Excision of choroid plexus, one side		Satisfactory. Head increased 4 cm. in 4 months	Returned for operation on other side; died in hospital from pyelitis, four days after admission
12 1921	17065	1 mo.		Phenolsulphonphthalein injected—unsatisfactory	Obstructive	Combined puncture showed obstruction	Cerebellar operation with opening of large cyst, inflammatory in nature		Discharged improved	Readmitted 6 weeks later for diarrhea which caused death 3 months after operation
13 1922	18981 S	4 mos.	F		Obstructive	Combined puncture	Suboccipital craniotomy. Fourth ventricle filled with red blood		Satisfactory	
14 1922	18679	9 mos.	F		Obstructive	Combined puncture	Cerebellar craniotomy relieving obstruction. Inflammatory		Died week later of pneumonia	

TABLE 1—*Continued*

CASE NO.	HOSPITAL NUMBER	AGE	SEX	DYE INJECTED	TYPE OF HYDROCEPHALUS	TESTS	TREATMENT USED	HARTMANN'S SOLUTION	RESULTS	COMMENT
15 1923	20255 M.S.	2 mos.	F		Communicating		Attempted excision of plexus-sessile; therefore cauterized with actual cautery		Died	
16 1923	21863	4 yrs.	F		Communicating	Double puncture	Cerebral craniotomy; internal hydrocephalus. Plexus exposed but not removed—not clear why		Uneventful recovery. No improvement	
17 1924	A-1918	1 mo.	F		Obstructive	Combined puncture	Cerebellar craniotomy. Congenital abnormality of cerebellum; vermis split to start cerebrospinal fluid		Patient shocked. Died 24 hours later	
18 1924	B-243	6 mos.	F		Obstructive	Combined puncture	Cerebellar craniotomy. Opening of obstructive cyst		Child shocked. Died 4 hours after operation. No transfusion	
19 1924	B-2621	1 yr.	F		Communicating		Head of extreme size; useless to attempt anything			
20 1925	B-1788	3 yrs.	M		Obstructive, following inflammation		Cerebellar exploration		Satisfactory	
21 1925	C-1792	8 mos.	M		Obstructive (?). Air injected through ventricle	Spinal air attempted, unsuccessful	Closed foramen of Monro opened. Excision of choroid plexus. Cerebellar exploration		Died	Autopsy showed cerebellar cyst and old temporal lobe abscess

22 1925	C-610	5 mos.	F	Treatment first with diuretin	Obstructive	Air injection; no air passed from one lateral ventricle to other	Occlusion of foramen of Monro; re-opened		No improvement	Lived for several years
23 1925	C-696	8 mos.	F	Treated with diuretin without effect	Communicating		Third ventriculostomy		Recovered	
24 1926	C-1775	7 wks.	M		Obstructive, due to inflammation and frontal cyst	Air injection. Left frontal cyst	Cerebellar craniotomy. Adhesions fourth ventricle		Satisfactory for 3 months	Stormy convalescence. Returned 1 month later, air injection repeated. Died 7 weeks later
25 1926	C-1860	4 mos.	M		Obstructive	Combined puncture showed complete block	Cerebellar craniotomy, fourth ventricle, with old yellowish clots		Patient suddenly died though good condition after operation	No autopsy
26 1927	E-127	4 mos.	F	Diuretin tried ineffectively	Obstructive	Ventriculogram	Cerebellar craniotomy with breaking-up of adhesions		Improved	
27 1927	D-1817	15 days	F		Communicating	Combined puncture	Head so enormous, useless to treat			
28 1928	E-2190	5 mos.	F		Obstructive. 48.5 cm. circumference	Combined puncture. Fluid rose equally. Air injection, 80 cc. fluid, turbid; temperature for almost 3 weeks	Choroid plexus sessile, excised. 6 clips; cortex cut with electric knife		Died 5 days after operation	
29 1928	E-1560	3 wks.	M		Communicating	Double puncture	Choroido-plexectomy excision		Developed diarrhea and died 7 weeks after operation	
30 1928	E-417	5 mos.	F		Obstructive	Double puncture	Cerebellar exploration, difficult because of plexus veins around base. Much bleeding		Much bleeding. No donor ready. Patient died on table	Would undoubtedly have been saved

TABLE 1—*Continued*

CASE NO.	HOSPITAL NUMBER	AGE	SEX	DYE INJECTED	TYPE OF HYDROCEPHALUS	TESTS	TREATMENT USED	HARTMANN'S SOLUTION	RESULTS	COMMENT
31 1929	F-2171	6 mos.	M	Diuretin ineffective	Communicating	Combined puncture	Coagulated plexus first time		Discharged improved	
32 1929	F-2028	5 mos.	F		Obstructive	Combined puncture showed block	Cerebellar exploration. Huge venous sinus found from which much blood lost		Patient died on table	Congenital closure of aqueduct of Sylvius
33 1929	F-684	7 mos.	F		Communicating (?), secondary to meningitis at 1 month	Combined puncture showed free communication	Choroid plexus coagulated		Satisfactory	Unable to follow up
34 1929	F-2089	3 mos.	F		Obstructive (?)	Double puncture. Result uncertain	Put on diuretin by Dr. Marriott			
35 1929	F-609	9½ mos.	M		Communicating	Double puncture	Choroido-plexectomy coagulation		Died 3 weeks later suddenly	
36 1929	F-1347	8 mos.	M	Diuretin tried but ineffective	Communicating	Double puncture	Choroido-plexectomy coagulation, troublesome intraventricular bleeding		Died of broncho-pneumonia 2 days later	
37 1929	F-1610	7 mos.	M		Communicating	Double puncture	Choroido-plexectomy		Died suddenly after operation—shock	
38 1930	G-1120	3 yrs.	M		Obstructive	No combined puncture	Cerebellar craniotomy with opening of obstructive cyst		Satisfactory	No follow up
39 1930	G-1310	6 mos.	F		Obstructive		Cerebellar craniotomy, relief of obstruction but cerebrospinal fluid continued to form, therefore choroido-plexectomy done		Satisfactory postoperatively	Death after 10 days from pneumonia

40 1930	G-2407	2 yrs.	M		Obstructive, postmeningitic or luetic		Cerebellar craniotomy with removal of inflammatory cyst		Recovery, good improvement	Child on antiluetic therapy, apparently luetic
41 1930	G-1858	6 mos.	M		Communicating	Combined puncture	Choroidoplexectomy one side. No relief. One month later, other side coagulation		Stormy course throughout both operations. Wound broke down after second	Patient died 18 days after operation of meningitis
42 1930	F-2359	3 yrs.	M		Obstructive	Air studies showed internal hydrocephalus one side, external hydrocephalus other side	No promising result from operation		Discharged	
43 1930	H-707	3 mos.	F		Obstructive	Combined puncture	Cerebellar craniotomy. Diagnosis not positive		Improved. Lumbar puncture after operation showed obstruction relieved	
44 1930	C-139	3 yrs.	M		Communicating	Double puncture. Air injection. Ventricles contained 400 cc. air	With fontanelles closed, no use to operate		Discharged	
45 1931	C-1879	10 wks.	M		Communicating (?)	No combined puncture	Meningitis, which cleared up. Operation after 3 months. Choroidoplexectomy, both sides coagulated at one time		Satisfactory at discharge	Died of laryngeal paralysis one year later
46 1931	H-1103	5 mos.	F		Communicating. Head 54 cm. (birth injury)		Coagulation plexus one side, other side 10 weeks later		Head stopped growing. Recovered	(Picture of wound 2 weeks after operation) Fig. 1

TABLE 1—*Continued*

CASE NO.	HOSPITAL NUMBER	AGE	SEX	DYE INJECTED	TYPE OF HYDROCEPHALUS	TESTS	TREATMENT USED	HARTMANN'S SOLUTION	RESULTS	COMMENT
47 1931	H-487	2 mos.	F		Obstructive	Combined puncture showed block	Probably congenital closure of aqueduct. Cerebellar craniotomy		Died	
48 1931	H-1761	5 yrs.	M		Obstructive	Combined puncture	Cerebellar craniotomy, obstruction not relieved		Died	Autopsy. Obstruction to aqueduct of Sylvius. Congenital anomaly
49 1931	H-1118	2 wks.	M		Communicating	Combined puncture	Choroid plexus coagulated		Discharged	Died 2 months later of pneumonia
50 1932	H-2557	3 mos.	F		Obstructive, post-meningitis	Combined puncture showed block	Cerebellar exploration with freeing adhesions. Obstruction not relieved. Returned 1 month later, reoperation; block now in aqueduct; new aqueduct made		No relief. Died 1 month after operation	
51 1932	I-737	2 mos.	F		Obstructive (?)	Combined puncture—partial block	Opened large obstructive cyst in vermis region. Reopened 6 weeks later. Donble choroid plexus	First use of Hartmann's solution	Satisfactory operation, uneventful. Died suddenly 24 hours later	
52 1932	I-1105	4 mos.	M		Communicating, 48 cm.		Choroid plexus coagulated; some bleeding with clots; removed	Hartmann's solution used	Blood transfusion, matching O. K. Sudden death; question of air embolus	

53 1933	J-301	4 mos.	M		Communicating	Double puncture	Choroid plexus coagulated, one month later on other side	Hartmann's solution used	Child followed for 3 months, head still enlarging	
54 1933	J-1795	4 yrs.	F		Obstructive		Cerebellar craniotomy; fourth ventricle contained clots and adherent cisterna magna		Satisfactory	
55 1933	J-1547	4 mos.	M		Obstructive	Combined puncture, complete block	Cerebellar craniotomy with relief of fourth ventricle obstruction by thick membrane		Died suddenly on table	Child had had hemorrhagic disease of newborn. Nothing unusual in operation; no loss of blood. Postmortem, enlarged thymus
56 1933	J-2704	3½ mos.	F		Communicating	Combined puncture	Choroidoplexectomy; two months later, second side	Hartmann's solution used	Four months later head not growing larger	
57 1933	K-363	6 mos.	F		Communicating	Combined puncture	Choroidoplexectomy, right and left	Hartmann's solution used	Following second operation, developed pressure sore on head; infection superficial. Did well but died 15 months later, cause unknown. Head had not enlarged	
58 1934	K-902	2 mos.	M		Obstructive	Combined puncture	Cerebellar craniotomy with removal of block. Ventricles collapsed when block relieved	Hartmann's solution used	Child died 1 hour after operation—shock	
59 1934	K-402	3 mos.	F		Communicating, secondary to closure of spina bifida at 1 month		Choroidoplexectomy, one side	Hartmann's solution used	Four years later child bright and walking	

TABLE 1—*Continued*

CASE NO.	HOSPITAL NUMBER	AGE	SEX	DYE INJECTED	TYPE OF HYDROCEPHALUS	TESTS	TREATMENT USED	HARTMANN'S SOLUTION	RESULTS	COMMENT
60 1934	K-410	14 mos.	F		Communicating	Combined puncture	Choroid plexus coagulated	Hartmann's solution used	Seven years later, child going around with help, goes to school, does well	
61 1934	K-2124	6 mos.	M	Diuretin tried for three months	Communicating	Double puncture	Choroidoplexectomy, bilateral, 1 month apart. Head still growing. Ureterospinal anastomosis. Had to be reopened several times	Hartmann's solution used	Seemed O. K. Died 2 months after discharge	Ascending infection
62 1934	K-2599	3 mos.	F		Communicating	Combined puncture. Air studies	Choroidoplexectomy one side, second side 1 month later	Hartmann's solution used	Died 4 days after operation of bronchopneumonia, and hydropericardium	
63 1934	K-2719	7 mos.	M		Communicating	Combined puncture	Choroid plexus coagulated	Hartmann's solution used	Four years later, child looks well, running around, talking normally	
64 1935	L-1583	4 mos.	M		Communicating	Combined puncture and air studies	Case for choroidoplexectomy or ureteroarachnoid anastomosis; did not drain; laminectomy reopened; catheter in ureter, drained cerebrospinal fluid but blood appeared in cerebrospinal fluid		Child died	Large hemorrhage in one ventricle probably due to injury of plexus by needle

65 1935	L-2092	3 mos.	F		Communicating	Double puncture	Bilateral choroidoplexectomy through one side	Hartmann's solution used	Wound healed but fever after operation. Died 17 days after operation	Autopsy showed meningitis; congenital occlusion of aqueduct
66 1936	M-556	8 yrs.	F		Obstructive	Complete air studies; 750 cc. fluid removed and air replaced by Hartmann's solution	Not operated upon	Hartmann's solution used	Reaction extreme and patient died 24 hours after air studies	Acute ependymitis
67 1936	M-1156	1½ yrs.	F		Communicating	Double puncture	Choroidoplexectomy one side	Hartmann's solution used	Satisfactory	Died 3 months later at home, cause not ascertained, seemed O. K. at discharge
68 1936	M-1784	1 yr.	M		Obstructive		Cerebellar craniotomy. Arachnoid cyst of cerebellum (large)	Hartmann's solution used	Good result	Report 1 year later, child running around, developing normally; head not enlarging
69 1936	M-2113	2 yrs.	F		Obstructive	Repeated air studies	Frontal craniotomy showed absent septum, open foramen of Monro	Hartmann's solution used	Satisfactory recovery	No improvement. Probably congenital stenosis of aqueduct as opening could not be identified
70 1936	M-1095	6 mos.	M		Communicating	Double puncture	Good case for choroidoplexectomy but developed pneumonia and sent home			Case lost sight of
71 1936	M-2040	4 yrs.	F		Congenital (?) Type undetermined	Air studies. Encephalogram	Upset on table, temperature never brought down		Died 7 days after procedure	

TABLE 1—*Continued*

CASE NO.	HOSPITAL NUMBER	AGE	SEX	DYE INJECTED	TYPE OF HYDROCEPHALUS	TESTS	TREATMENT USED	HARTMANN'S SOLUTION	RESULTS	COMMENT
72 1936	M-800	3 mos.	F		Communicating	Double puncture	Bilateral choroidoplexectomy, 2 months apart	Hartmann's solution used at second operation. Marked temperature reaction, solution made up wrong, too much acid	One year later, developing but slowly	
73 1936	M-877	2 mos.	F		Communicating	Double puncture	Choroidoplexectomy, one side	Hartmann's solution used	Child did well; head enlarged 3 cm. in one year	One year later developed diarrhea and middle ear infection and died
74 1936	M-1121	5 wks.	F		Communicating	Double puncture	Choroidoplexectomy; 3 months later, other side. Ureterospinal anastomosis at 11 months	Hartmann's solution used	Five months after last operation, head not enlarging	
75 1937	N-1319	4 mos.	F		Obstructive	Combined puncture repeatedly tried; never able to get fluid from spinal canal; 2 cc. lipiodol into ventricle, went from one ventricle to other and into third but apparently obstruction of aqueduct. New aqueduct made with catheter, no relief	Third ventriculostomy	Hartmann's solution used	When seen 2 months later, O. K.	

76 1937	K-730	5 yrs.	M		Obstructive, postmeningitic	Combined puncture	Cerebellar craniotomy; adhesions broken up. Month after discharge showed free communication; obstructive changed to communicating type. Choroidoplexectomy attempted, one side only coagulated, other bound down by adhesions. Uretero-arachnoid anastomosis	Hartmann's solution used	Symptoms relieved. Progressing nicely	
77 1937	N-1672	1 mo.	F		Communicating	Combined puncture	Choroidoplexectomy one side. Very thin cortex, question if enough for normal development	Hartmann's solution used	Satisfactory	Two years later child walking, talking a little, gait somewhat scissors in type. Mental deficient 3 years after operation
78 1937	N-1709	5 mos.	F (col.)	(N. B. Seen at 5 weeks, had strep. viridans in ventricle, cleared up)	Obstructive		Cerebellar craniotomy, freed adhesions, opened membrane closing iter, and excised vermis into fourth ventricle. Second attempt, third ventriculostomy		Hydrocephalus continued	Absorption mechanism destroyed

TABLE 1—*Continued*

CASE NO.	HOSPITAL NUMBER	AGE	SEX	DYE INJECTED	TYPE OF HYDROCEPHALUS	TESTS	TREATMENT USED	HARTMANN'S SOLUTION	RESULTS	COMMENT
79 1937	N-1410	6 mos.	F		Communicating	Double puncture	Bilateral choroidoplexectomy, 1 month apart	Hartmann's solution used	Child did well	Readmitted 2 years and 4 months later; recently head had started to grow. Puncture of ventricle showed fresh blood, indicating hemorrhage, cause unknown. Died
80 1938	O-1560	1 yr.	F		Communicating	Combined puncture	Bilateral choroidoplexectomy; first side, difficult and some intraventricular bleeding though second side O. K. Bleeding probably factor in death	Hartmann's solution used	Died	
81 1938	O-1063	6 wks.	F		Due to congenital anomaly of skull		No operative indications			
82 1938	O-1903	8 wks.	M		Communicating	Double puncture; much upset by ventricular air studies which were unnecessary	Bilateral choroidoplexectomy through one	Hartmann's solution used	Child never did well; emaciated; died 7 weeks after operation	
83 1939	P-981	3 mos.	M		Communicating, and spina bifida		Exploration of posterior fossa for Arnold Chiari defect		Died	

84 1939	P-1392	3½ mos.	F		Communicating	Combined puncture	Absent septum. Bilateral choroido-plexectomy through one incision		Developed postoperative diarrhea, died 2 weeks after operation	
85 1939	P-784	6 mos.	F		Obstructive		1st, cerebellar operation with attempted relief of obstruction; then bilateral choroidoplexectomy 1 month apart	Hartmann's solution used	Child died after third operation, had some bleeding and injured thalamus	
86 1939	P-1743	2 mos.	F		Communicating	Combined puncture did not work; air studies made	Choroido-plexectomy, one side	Hartmann's solution used	Did well	Report 16 months later, beginning to talk
87 1939	P-2107	6 mos	M		Communicating	Combined puncture	Bilateral choroido-plexectomy through one side	Hartmann's solution used	Did well	Developed some intestinal infection and died 1 year later; hydrocephalus had been arrested
88 1940	Q-1882	5 mos.	M		Communicating	Combined puncture	Choroido-plexectomy		Postoperative broncho-pneumonia, very weak	Died 1 month after getting home
89 1940	Q-185	4½ mos.	F		Communicating	Double puncture	Bilateral choroido-plexectomy done three weeks apart	Hartmann's solution used		Report 3 months later, doing well
90 1940	Q-2453	1 day	F		Communicating, and spina bifida		Spina bifida repaired. Bilateral choroido-plexectomy	Hartmann's solution used	Hydrocephalus arrested. Child developing well but paralyzed from waist down	This procedure seemed unwise since the child will grow up paralyzed but the family wanted the operation

TABLE 1—*Concluded*

CASE NO.	HOSPITAL NUMBER	AGE	SEX	DYE INJECTED	TYPE OF HYDROCEPHALUS	TESTS	TREATMENT USED	HARTMANN'S SOLUTION	RESULTS	COMMENT
91 1940	P-981	3 mos.	M		Communicating, and spina bifida		Cerebellar exploration to see if Arnold Chiari defect. None found		Died	
92 1940	Q-202	1 day	F		Communicating and cerebral meningocele		Meningocele closed. Choroidoplexectomy 1 month later	Hartmann's solution used	Head not enlarging. Satisfactory result	In this case clearly the problem was to control hypersecretion
93 1940	Q-1852	4 mos.	F		Communicating and myelomeningocele		Spina bifida healed over. Choroidoplexectomy	Hartmann's solution used	Child doing well. Head not enlarging	Done at request of family
94 1940	Q-740	2 mos.	F		Communicating, and myelomeningocele		Repair meningocele. Bilateral choroidoplexectomy at one time 2 months later	Hartmann's solution used	Died	
95 1940	Q-554	11 days	M		Communicating and myelomeningocele		Repair of spina bifida. Choroidoplexectomy, one side	Hartmann's solution used	Improving. Normal development	
96 1940	Q-185	4½ mos.	F		Communicating, following a birth hemorrhage	Combined puncture	Bilateral choroidoplexectomy	Hartmann's solution used	Arrested. Doing nicely. Developing slowly 1 year later	
97 1940	Q-1945	8 mos.	F		Communicating	Double puncture	Air studies. No operation		Died. Pneumonia	
98 1940	Q-1882	5 mos.	M		Communicating	Double puncture	Ventriculogram. Choroidoplexectomy	Hartmann's solution used	Not arrested	Died from bronchopneumonia at home 1 month later

TABLE 2

Summary of cases

Communicating hydrocephalus	54	cases
Recoveries	22	
Deaths	27*	
Not operated upon	5	(1 death)†
Operations		
Choroidoplexectomy	55	
Removal of both plexuses at one operation	6	
Unilateral choroidoplexectomy	23	
Bilateral choroidoplexectomy (13 cases)	26	
Third ventriculostomy	1	
Uretero-arachnoid anastomosis	2	
Cerebellar craniotomy	2	
Cerebellar craniotomy for Arnold Chiari defect	1	

* 6 deaths not connected with operation:
Case 11—4 months after operation returned to hospital; died of pyelitis.
Case 45—1 year later died of laryngeal paralysis.
Case 57—15 months later head had not enlarged. Died, cause unknown.
Case 73—died 1 year later of diarrhea and middle ear infection.
Case 79—arrested for 2 years and 4 months, then died of intraventricular hemorrhage.
Case 87—arrested hydrocephalus; 1 year later died of intestinal infection.

† 5 cases not operated upon:
2—head too large to operate upon.
1—fontanelle closed.
1—developed pneumonia, did not return for operation.
1—died of pneumonia, without operation.

Obstructive hydrocephalus	42	cases
Recoveries	18	
Deaths	21	
Not operated upon	3*	(1 death)
Operations		
Corpus callosum puncture	1	
Cerebellar craniotomy with relief of obstruction	31	
Choroidoplexectomy	7	
Double removal at one operation	1	
Craniotomy with opening of foramen of Monro	2	
Cerebellar craniotomy for closure of aqueduct of Sylvius	3	
Third ventriculostomy	2	

* 3 cases not operated upon:
1—treated with Diuretin (Case 34).
2—heat upset following air injection (Cases 66 & 71).

Unclassified		
Number of cases	2.	

the communicating type of hydrocephalus, the ultimate prognosis is good if the case is not too far advanced. Just how much a cortex can be compressed and still function normally is difficult to answer but we know from our experience

with cerebellar tumors in children that ventricles may be enlarged so that they contain several hundred cubic centimeters of cerebrospinal fluid and still these children, after their tumor has been removed, develop normally and have no disturbance in their mentality.

Congenital anomalies, such as described by D'Errico (6), have been rare in this series. There have been only three cases, 17, 81, 83.

Another point of interest is how often abnormalities of the cortex are present—microgyria. It certainly would be inadvisable to operate upon a case knowing microgyria was present. There is no way of determining this point other than inspecting the cortex as we do in our operation. From a prognostic point of view, it is of great importance to know this and this cannot be determined when using the method of Putnam or Scarff or Dandy. Microgyria has not been noted in our cases in which the cerebral cortex has been exposed for a choroidoplexectomy. It does, of course, occur but usually in those cases associated with ex-

Fig. 3. This is Case 63, who had an unilateral choroidoplexectomy. The boy is now almost eight years old and is developing perfectly normally. His head is somewhat larger than that of a child of his age.

treme forms of spina bifida. In our series, we have only operated upon a few cases of hydrocephalus that developed after a spina bifida had been operated upon. Cases 11, 59, 83, 90, 92, 93, 94, 95.

CONCLUSIONS

A study of these cases seems to warrant the following conclusions:

1. All hydrocephalics fall into one of two classes, the communicating and the obstructive.

2. A satisfactory way of differentiating them is by the double puncture method.

3. All cases should be operated upon before the hydrocephalus has become too large so that treatment can be instituted before permanent damage to the cortex has taken place.

4. The only effective way of treating communicating hydrocephalics is by destroying the choroid plexus.

5. The best way of destroying the plexus is by electro-coagulation.

6. The operative procedure is made much safer by making use of artificial cerebrospinal fluid (Hartmann's solution).

7. The treatment of obstructive hydrocephalus consists in relieving the obstruction and then trying to keep the obstruction from reforming. This may be accomplished by early repeated lumbar punctures.

8. If hydrocephalus continues after the relief of obstructive hydrocephalus, no very effective method of dealing with the situation is at our disposal.

9. Congenital deformities in this series have rarely been found and would warrant the conclusion that they are infrequently the cause of hydrocephalus.

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THE TYPE OF PERSONALITY SUSCEPTIBLE TO PARKINSON DISEASE

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Non-infectious, idiopathic or arteriosclerotic Parkinson disease has held the interest of neurologists since Parkinson first described this syndrome. While considerable progress has been made in understanding the pathologic process and its anatomical localization as well as in management of the patient, the cause of this disorder is still obscure and unknown. During the past twenty-five years I have met a reasonably large number of such patients in my work at various hospitals and I have been impressed by the fact that there is a definite type of personality that is likely to develop this disorder.

My attention was called to this type of personality by an intelligent and educated social service worker whose mother was a patient in the Montefiore Hospital when I was Resident in Neurology there. She constantly spoke of the change in the emotional reaction of her mother following the onset of the illness. Prior to her illness, the patient was apparently well-poised, calm, solicitous about the welfare of others and almost self-effacing. However, after the onset of her illness she became a complaining and dissatisfied person who would complain about the nurses and the doctors and about the care that she was receiving in the hospital. She never asked about the welfare of the members of her own family or of her freiends, but her entire conversation was occupied with complaints. In studying the personality of that particular patient I learned that the description given to me by her daughter was only partly correct. The patient said that when she was well she was apparently calm and seemed almost indifferent to critical situations at home, but in reality, she was invariably in a constant state of anxiety and worry but would conceal this from her relatives. Since then, in observing a reasonably large number of patients suffering from the idiopathic form of paralysis agitans, and to a lesser extent those that show arteriosclerotic manifestations, I have been impressed by the peculiar type of personality which later develops the Parkinson syndrome, and which I have designated as the "masked personality."

In analyzing this personality, the following traits are to be noted:

1) They possess normal or superior intelligence.

2) In their method of adaptation, they pursue a path of conduct which is of a socially approved character. They comprise a group which may be designated as "virtuous." They are law-abiding citizens, who give much of their time to their homes and to their families. They are aggressive and generally successful in their undertakings. They are regarded as trustworthy and as exemplary citizens. While sexually quite aggressive, they confine their intimacies to their lawful partners. Their homes and their families seem to be the center of their life's drive. In their particular work, their successes are due to their diligence,

perseverance and thoroughness, and not to dishonorable dealings. Whenever any task is to be performed, nothing seems to stand in the way of its completion. There is no procrastination and there is no delay. The task has to be completed, and as speedily as possible. They are indefatigable workers. They do not seem to entertain any grudge, though they never forget an injustice done to them. Outbursts of temper may occur but do not last very long.

3) Whenever there is any difficulty or problem at home, they are the ones to whom the problem is brought for its solution. They seem to have such a calm exterior that they soon become the emotional prop for many who are in difficulties. Anything of an unpleasant or difficult nature does not seem to upset them. The illness of a child, death of the wife, sickness or death in the family, or other serious circumstances, appear to make no impression upon them. They rarely appear to be demonstrative and yet they are the ones who directly or indirectly guide the destinies of most members of their families or of others dependent upon them. Because of this outward manifestation of calmness and poise, they attract those who need help and guidance. In their immediate social groups, they are the ones to whom people come for advice and guidance. In any social organization to which they may belong, they invariable hold positions of trust and responsibility. These honors are conferred upon them because they impress others with their integrity and qualities of leadership. However, when interviewing these people, one elicits a different story from them; viz: that they are always in a state of emotional tension, that they are ever brooding and constantly worrying over any problem that may confront them, members of their families, or those dependent upon them. In case of illness, business reverses, or other similar situations, they find themselves in a state of emotional tension and anxiety closely bordering upon panic. Nevertheless, they control themselves, and they conceal their inner feelings so that to the outsider they appear calm, well-poised and almost indifferent to the situation. In simpler terminology, these individuals have learned at first to suppress and later to repress emotional reactions to the extent of successfully concealing the continuous turmoil that exists within them. In other words, they have what I designate as a "masked personality." It is this constant repression of emotional and instinctive drives that comprises the nucleus of their masked personality.

In order to repress these tendencies to which the average person gives fairly free expression, it is quite obvious that certain reflex arcs are established in which the cortex, the basal ganglia and their associated centers, the hypothalamus and the thalamus, participate. It is reasonable to assume that physiologic activity is intense in many of these parts of the brain, particularly in the field of circulation, and certain microscopic and chemical alterations may occur in these regions which, at first cannot be detected, even under the modern histopathologic investigations. As long as repression is maintained along anatomically and physiologically intact neuronal pathways, health is preserved. Sooner or later, as a result of intense overactivity along these structures and pathways, classical degenerative changes characteristic of this disorder ensue, and then there occurs failure of repressing emotional expressions, and clinical Parkinsonism in the

idiopathic or even arteriosclerotic form develops. We know that in a reasonably large number of patients clinical Parkinsonism may follow an emotional or physical trauma, which may be interpreted as failure to repress overt emotional reactions. We also know that this disorder occurs more in males than in females, and it is quite apparent that in their struggle for existence, greater demands are made upon men than on women. It is also a fact that this disorder is hardly ever encountered in primitive people, on whom less demands are made for their adaptation because of their simpler life. Moreover, it has been repeatedly called to our attention, in an effort to correlate anatomical findings with physiological manifestations and clinical signs and symptoms, that not all these centers need be involved, but that some link in this chain when affected may produce a disordered physiologic organism. Once Parkinsonism is established, the process is not a reversible one and symptoms continue to develop despite all efforts at therapy.

The clinically Parkinson patient presents a personality which is just the opposite of his normal self. He is a complaining individual, who makes excessive demands upon all with whom he comes into contact. He appears to be self-conscious, self-centered and hardly appreciative of what is done for him. Evidently, there has been a release in that mechanism which previously had been successful in masking his inner feelings and emotions.

During the past decade I have had occasion to observe four people whom I have known for over a quarter of a century and who possessed the type of personality I have just described. Each one of them has developed clinical Parkinsonism.

The value of the recognition of the existence of a "masked personality" rests on the fact that it affords an opportunity for preventive therapy. People showing this type of personality, if recognized very early, should be taught to give reasonably free expression to their worries, fears and anxieties and thus prevent the development of clinically idiopathic or to a lesser degree, arteriosclerotic, Parkinsonism.

CHEMICAL DIFFERENTIATION OF TAY-SACHS DISEASE AND OTHER LIPOIDOSES

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Various types of lipoidoses have been described in the past decades. The incidence of these ailments is relatively low, most of them are of rare occurrence; but the errors of lipoid metabolism inherent in these conditions command the attention and interest of clinician, pathological anatomist and physiological chemist in equal measure.

Certain lipoid substances, instead of completing their natural metabolic cycle, accumulate in various sites of the body. These infiltrations and tumors occur in the viscera, the central nervous system, the integument, and the skeleton, and are thus apt to impede and disturb, according to curious patterns, an array of functions ranging from posture to hormonal regulations, from the performance of the sense organs to metabolic tasks. In contrast to these heterogeneous clinical manifestations, a superficial similarity obtains in the histological aspects of tissue response to these abnormal lipoid deposits which give rise to "giant" or "foam" cells. Further inspection reveals, of course, certain differences in histologic appearance, but the detection of striking and significant peculiarities has been left to chemical analysis of the lipoids.

Table 1 lists the nature of the lipoids, which characterize the various lipoidoses, and indicates the *loci* of their accumulation. The lipoids found conform as a rule in type to those present in normal animal organs. This statement deserves particular emphasis in the case of Tay-Sachs disease where a new substance provisionally designated "substance X" was recently discovered as the characteristic lipoid (1, 2). This compound is closely related to the cerebrosides with which it has the following constituents in common: sphingosine, galactose, and one molecule of fatty acid. But while this exhausts the composition of the cerebrosides, substance X contains in addition the unstable, but characteristic amino acid neuramic acid (3, 4). But for its accumulation in amounts of 4 to 8 per cent of the total solids in Tay-Sachs brain this new amino acid would have remained unnoticed. In fact, a subsequent investigation of normal brains of the same age group revealed the presence of substance X in amounts of 0.3 per cent (4); it is typical for the gray matter and not found in the white matter (5). In a related condition designated "juvenile type of amaurotic idiocy" values up to 1.5 per cent substance X are given by Klenk and in Niemann-Pick disease he found 1.5 to 2.4 per cent. The latter figures range between those found in normal brain and those in unequivocal cases of Tay-Sachs disease, suggesting a certain overlapping of Tay-Sachs characteristics into the Niemann-Pick group. However, the salient chemical feature of Niemann-Pick disease, viz. the increase in diaminophosphatides, is absent in typical Tay-Sachs cases or even reversed into a decrease.

In collaboration with Epstein and Lichtenstein (7, 8), we have studied the lipoids of spleen, liver and brain in a case of Niemann-Pick disease associated with Tay-Sachs disease. A signal increase in phosphatides was observed and we commented on the high N/P quotient, especially of the less soluble phosphatide-cerebroside fractions. We could not decide then whether this was due to a high content of cerebrosides or of polyamino phosphatides, but noticed a relatively small amount of sugar obtained on hydrolysis. Similar observations were made by Kahn in another case of Niemann-Pick disease (9). Klenk (10, 11) in a case of typical Niemann-Pick disease was able to isolate sphingomyelin as the typical accumulation product in brain, spleen and liver, a finding since confirmed in numerous instances. He furthermore found that the sphingomyelin in the brain of Niemann-Pick disease differed from the visceral sphingomyelin by containing almost pure stearic acid as its fatty acid constituent (11).

This observation exemplifies divergencies between the composition of pathologically accumulated lipoids from the normal representatives of the same type of lipoids. The most important example for such a qualitative deviation, how-

TABLE 1

Type and distribution of lipoids in lipoidoses

DISEASE	ORGAN	TYPE OF LIPOID ACCUMULATED	TYPE OF LIPOID DECREASED
Tay-Sachs	Brain	Substance X	Sphingomyelin
Niemann-Pick	Spleen and liver	Sphingomyelin	Neutral fat
Niemann-Pick	Brain	Substance X; "stearo"-sphingomyelin	Neutral fat
Gaucher	Spleen and liver	Cerebroglucosides and kerasin (?) (fatty acids C_{16}–C_{24})	—
Schüller-Christian	Various sites	Cholesterol; cholesterol esters and carotenoids	—

ever, has recently been given by Halliday (12) in Gaucher's disease. Here, the typical substance, accumulated in spleen and liver had been described by Lieb (13) as the cerebroside kerasine which consists of sphingosine, lignoceric acid and galactose. This cerebroside occurs in normal tissue, accompanying phrenosine, another cerebro-galactoside containing cerebronic instead of lignoceric acid. Halliday, however, was able to identify glucose as the sugar in the cerebroside of a Gaucher spleen. This finding was confirmed by selective fermentation, optical rotation and osazone preparation, and casts doubt on Lieb's and other older authors' analyses whose proof for the presence of galactose was meager. We consider it likely that the viscera in all cases of Gaucher's disease contain the cerebro-glucoside rather than the cerebro-galactoside. It is of interest to note that we (14) identified the sugar from the visceral cerebroside in Niemann-Pick disease as galactose by preparation of the osazone and observation of the downward mutarotation of the latter according to Levene (15).

Klenk (2) found that the cerebro-glucosides, typically accumulated in Gaucher viscera, contain every even numbered saturated fatty acid from C_{16} to C_{24},

whereas the brain cerebrosides were of the normal type with the C_{24} fatty acid predominanting. The brain cerebrosides ran also true to the normal pattern inasmuch as they were galactosides.

It is still impossible to recognize the physiologic meaning of these quantitative and qualitative deviations from normal in the organ lipoids in lipoidoses. The chemical knowledge, while most pertinent for future etiologic considerations, has not yet risen above a descriptive level. Accumulation of normal lipoids in earliest childhood as encountered in Tay-Sachs and Niemann-Pick disease is obviously a manifestation of a degenerative error in metabolism. On the other hand in Gaucher's disease, a condition developing in individuals of varying age, the visceral lipoids deviate from normal in quality as well as in quantity, yet this circumstance leaves the question open as to the innate or acquired character of Gaucher's disease.

TABLE 2

Interrelationship of tissue lipoids (ref. 14, 16)

Schüller-Christian	Cholesterol	
	Cholesterol + Fatty acid	Cholesterol esters
	Fatty acid + Glycerol + 2 mol. fatty acid	Neutral fat
	Glycerol + 2 mol. fatty acid + Phosphoric acid + choline	Lecithin
Niemann-Pick	Phosphoric acid + choline + Sphingosine + lignoceric acid	Sphingomyelin
Gaucher	Sphingosine + lignoceric acid + Galactose or glucose	Kerasin or cerebroglucoside
Tay-Sachs	Sphingosine + lignoceric acid + Galactose + Neuramic acid	Substance X

Aside from the puzzle presented by such abnormal lipoids with a configurationally different sugar component we are still ignorant of the significance attributable to the varying number of carbon atoms in the fatty acids concerned. Yet, it is remarkable how the lipoid types of animal tissues are intimately interlocked through the presence of common groups as exemplified in the following scheme.

It is plausible that their conversion into each other is brought about by the hydrolytic and synthetic activity of lipolytic enzymes, a process which we have designated as "exchange esterification" or "transesterification" (14,16). Hepatic esterase is the most familiar representative of lipolytic enzymes in the organs under scrutiny. We therefore compared the quantity of esterase in livers from various types of lipoidosis with that in normal livers in cases of accidental death. The esterase values (E.V.), a conventional measure of enzymatic activity were 1.76, 1.60 and 1.42 in the control cases, 0.69, 0.27, 0.23 and 0.80 in four cases of Gaucher's disease, 0.27 in a case of Schüller-Christian disease, while no enzy-

matic activity at all was detectable in a Niemann-Pick liver. The test substrate methyl butyrate is a simpler ester than the tissue lipoids in question but we have reason to believe in a close relationship between various lipolytic enzymes. E.g., the injection of pancreatic lipase into rabbits increases the amount of esterase in the liver which suggests the interconvertibility of one of these enzymes into another (17); from this and other evidence an even closer connection between esterase and more complex lipoidases, both intracellular enzymes, becomes plausible.

The above figures indicate a functional disturbance of the lipolytic and—because of the wellknown reversibility of enzyme reactions—of the lipopoietic mechanism in lipoidoses. This isolated metabolic observation, taken in conjunction with the chemical specificity of the lipoids accumulating in the various disease entities, may be of aid in a future elucidation of the etiology of lipoidoses.

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THE BIOCHEMISTRY OF THE LIPOIDOSES[1]

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The lipoidoses are a group of diseases characterized by the deposition of abnormally large quantities of fatty substances in the tissues. This accumulation of lipids must in the ultimate analysis be the result either of overproduction or underutilization, or of both, and the lipoidoses may, therefore, be included with those diseases which have been called "metabolic errors." Since, as you know, the study of such conditions has been fruitful in leading to an understanding of the processes of normal metabolism, investigators in the field of lipid biochemistry have been interested in the lipoidoses because of the hope that from their study some of the mysteries of normal lipid metabolism might be revealed. This hope has not been realized to any important degree as yet, although recently the existence of two new lipids, at least one of which appears to be a normal constituent of brain, was discovered during investigations of the lipoidoses.

The literature in this field is large and it would be quite impossible to review it comprehensively in a single lecture, even if I were qualified, as I am not, to discuss these diseases from the clinical and pathological standpoints. It was necessary, therefore, to select some part of the subject for consideration, and I have chosen that phase with which I am most familiar: the biochemistry of the lipoidoses. I do not think it is necessary to apologize for discussing the lipoidoses from the biochemical point of view before an audience made up predominantly of clinicians, because that approach goes to the very heart of what I believe to be the primary problem of lipoidosis; i.e., what is the mechanism by which the lipids accumulate in the tissues? Only after that question has been answered may rational and successful treatments of these diseases be anticipated. As yet, I regret to say, the answer has not been found; the underlying mechanism, or mechanisms, of the lipoidoses remains a complete mystery.

I shall not only restrict myself to the biochemical aspects of the subject but also, for the most part, to recent advances in this field. I shall summarize separately the developments of the past few years in the study of each of these diseases, and I shall then conclude with some general and speculative remarks concerning various hypotheses which have been advanced to explain the etiology of the lipoidoses.

Niemann-Pick disease. It makes little difference in what order the lipoidoses are discussed; I shall begin with Niemann-Pick disease because from its study perhaps the most important recent finding in this field has emerged. It has been known for some time that this disease is characterized by the deposition of phospholipids in the spleen, liver, brain, and other organs, and until 1934 lecithin and cephalin were thought to be chiefly involved; but in that year Klenk (1)

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made the highly significant discovery that the predominant lipid in a Niemann-Pick spleen was sphingomyelin. Klenk isolated in purified form an amount of sphingomyelin equivalent to 13 per cent of the dry spleen and considerably more doubtless was present (Table I). This represents an enormous increase over the small quantity of this fraction in the normal organ. In 1935 Klenk (2) reported analyses of the liver and brain from the same patient. Here too, as will be seen in Table I a remarkable accumulation of sphingomyelin was found.

Klenk's findings in this case were of outstanding interest and significance not only in demonstrating that sphingomyelin, and not the glycerol phospholipids, was the principal fatty substance deposited, but also in showing no increase at all above normal in lecithin and cephalin concentration. Furthermore there was no increase in any of the other lipid fractions with the possible exception of Substance X, the occurrence of which in the brain I shall discuss later. The deposition of large quantities of sphingomyelin in the tissues in Niemann-Pick disease has been confirmed by Tropp and Eckardt (3, 4), Teunissen (5), Teunissen and den Ouden (6), Thannhauser, Benotti, and Reinstein (7), Chargaff (8), and by Klenk himself in three other patients (9). There can be no doubt that

TABLE I

Lipids of organs in a case of Niemann-Pick disease

ORGAN	FAT + CHOLESTEROL	GLYCEROL PHOSPHOLIPIDS	CRUDE SPHINGOMYELIN	PURIFIED SPHINGOMYELIN
Spleen	6.4	8.6	23.5	13.0
Liver	8.7	11.6	24.6	15.6
Brain	15.1	15.1	23.5	7.6

Adapted from the data of Klenk (2).
All data represent percentage of dry tissue.

in Niemann-Pick disease there is a primary disturbance of sphingomyelin metabolism.

Klenk's findings in the three Niemann-Pick brains which he studied are shown in Table II. Although the very difficult separation of the protagon fraction into sphingomyelin and cerebrosides was not quantitative and the values shown are minimal, it is clear that sphingomyelin was the predominant constituent, being present in a concentration at least two to four times that found in a normal brain from an infant of approximately the same age. At the same time the cerebrosides were considerably reduced below the normal level.

Another finding of considerable theoretical importance was made by Klenk in an investigation of the fatty acids obtained from the sphingomyelin fractions of the original patient. Whereas lignoceric, nervonic, palmitic, and stearic acids were identified in the spleen and liver sphingomyelin, only stearic acid could be detected in the fraction from brain. This is the first time that a reasonably pure single sphingomyelin has been isolated from natural sources. Tropp and Eckardt (4) reported a similar difference between the sphingomyelins of spleen and liver on the one hand and of brain on the other in a patient with Niemann-

Pick disease, although they found a small proportion of palmitic and lignoceric acids along with stearic acid in the brain fraction.

In some of the relatively few case reports of this rare disease determinations of blood constituents have been included. By far the most comprehensive study both pre- and post-mortem, is that (10) of the patient in whom sphingomyelin deposition was first discovered by Klenk. The Swiss physicians Baumann and Scheidegger, whose patient this was, applied the techniques of modern medicine and allied sciences to a thorough investigation. Although some deviations from normal were found in the metabolic and biochemical picture, most if not all of these were probably secondary to the profound lesions of this disease. The same is true of other reports in the literature. For instance the ratio of combined to

TABLE II

Lipids of the brain in lipoidoses

DIAGNOSIS	FAT + CHOLESTEROL	GLYCEROL PHOSPHOLIPIDS	PROTAGON	PURIFIED SPHINGOMYELIN	CEREBROSIDES	SUBSTANCE X
Normal—13 mo.	8	23	8	1.9	1.5	0.3
Niemann-Pick	13	17	24	7.6	0.3	2.4
	9	15	17	4.3	0.7	1.5
	10	18	18	7.0	0.3	1.5
Tay-Sachs	10	15	13	0.4	0.6	4.3
	10	18	12	1.1	0.2	4.2
	25	6	27	trace	0.4	8.5
Juvenile amaurotic idiocy	15	23	10	1.1	1.3	0.2
	13	17	11	1.5	2.0	1.0
	13	22	12	1.1	1.9	1.5
	12	21	12	1.5	1.2	1.1
	11	—	12	2.3	2.3	0.4

Adapted from the data of Klenk (9, 11).
All data represent percentage of dry brain.

free cholesterol in the blood serum is usually low as would be expected in the presence of extensive liver damage. However, most authors have found the total cholesterol concentration to be within normal limits and no evidence for an increased concentration of sphingomyelin in the blood in Niemann-Pick disease was obtained by Baumann, Klenk, and Scheidegger (10), Thannhauser, Benotti, and Reinstein (7), or by Chargaff (8).

Tay-Sachs disease (*amaurotic idiocy, infantile type*). The findings described in the preceding section have provided a decisive answer to the long-debated question: are Niemann-Pick and Tay-Sachs diseases variant forms of the same malady? Despite some marked differences between these two lipoidoses, such as the absence of lipid deposition in the liver and spleen in amaurotic idiocy, some have thought that they were basically the same with the disturbance limited to

the brain in Tay-Sachs disease. Analyses of three Tay-Sachs brains by Klenk (9, 11) (Table II) show that this is not correct. Whereas, as we have seen, the Niemann-Pick brain is characterized by a marked deposition of sphingomyelin, there was no increase in this lipid fraction in Tay-Sachs disease; on the contrary there was a substantial decrease.

Klenk found another biochemical difference between the two diseases. In his fractionation of the brain lipids from the first Niemann-Pick patient he separated a new substance behaving in some respects like a cerebroside. This fraction, which Klenk called Substance X, was found in large quantity in Tay-Sachs brains in which it comprised the major constituent of the protagon fraction. It is highly unstable and difficult to isolate as evidenced by the fact that it had been overlooked by previous investigators. Undoubtedly the values in Table II represent only a portion of the amount actually present. It appears that in Tay-Sachs disease there is a primary disturbance in the metabolism of Substance X just as in Niemann-Pick disease there is a primary disturbance in the metabolism of sphingomyelin.

The existence of Substance X was confirmed by Blix (12) who isolated it from normal brain. About a year ago Klenk (13) described it in more detail on the basis of studies carried out on a fraction which he also obtained from normal brain. No differences between the products from Tay-Sachs and normal brains were observed. The split products are fatty acids, sphingosine, or a base very similar to sphingosine, galactose, and an hitherto unknown nitrogen-containing organic acid which Klenk named neuramic acid. The first three substances are those yielded by cerebrosides and Substance X appears, therefore, to be of cerebroside type, but to differ from the known cerebrosides in containing neuramic acid. The most characteristic property of this new lipid constituent is that of being exceedingly labile in aqueous inorganic acids in which it is destroyed with the formation of a carbonaceous, humin-like substance. It is because of this property that Substance X was not recognized before. It is also characterized by yielding a color with the Bial reagent. The reaction is very sensitive and may be applied to the quantitative determination of as little as 10 to 20 γ of the stubstance; a property which should make Substance X one of the easiest lipids to study metabolically even though it is perhaps the most difficult to isolate. Thus the investigation of the lipoidoses has led to the isolation and partial identification of a new fatty substance, which, since it is present in normal brain, may well prove to be of importance in normal metabolism.

Amaurotic idiocy, juvenile type. This condition has been little studied from the biochemical standpoint. The only analyses are those which were reported by Klenk on five brains (Table II) and which showed no definite and consistent increase in any of the lipid fractions. The higher values for protagon and its constituents as compared with the normal brain are probably not related to the disease but to the normal increase with age in the process of myelination.

Gaucher's disease. Like Niemann-Pick disease, which it resembles in several ways, Gaucher's disease is characterized by the deposition of large quantities of a lipid in various tissues, especially in the spleen and liver. In 1924 Lieb (14)

identified the fatty substance which accumulated in a Gaucher spleen as a cerebroside. In its physical properties and in the products which it yielded on hydrolysis, namely, lignoceric acid, sphingosine, and galactose, it appeared to be identical with kerasin, one of the cerebrosides occurring in brain. Since then several investigators who have isolated this substance from various organs of patients with Gaucher's disease have, in agreement with Lieb, designated it as kerasin, relying in the main on physical properties, especially the selenite test of Rosenheim (15), for its identification.

In 1940 Halliday, Deuel, Tragerman, and Ward (16) made the important discovery that the cerebroside isolated from a Gaucher spleen contained glucose rather than galactose. They proved this conclusively by showing that the sugar was fermented completely by yeast; that it yielded glucosazone, as shown by crystalline form and melting point; that it failed to give a mucic acid test; and that it was completely destroyed by a culture of *Proteus vulgaris* which did not attack galactose, fructose, or mannose, but which did largely destroy glucose. The carbohydrate prepared from the cerebrosides of a normal brain was carried through these tests simultaneously and was found to behave like galactose in contrast to the sugar from the Gaucher spleen.

Later in the same year Klenk (11), stimulated by the report of Deuel and his colleagues, published a detailed investigation of the cerebrosides from the spleen of one patient with Gaucher's Disease, and from the spleen, liver, and lungs of another. The results were in complete agreement with Deuel's finding; the carbohydrate present in each of these samples of cerebroside was pure glucose as shown by complete fermentation by yeast, by the specific rotation, and by the formation of glucosazone.

It may be concluded that in three authentic cases of Gaucher's disease the lipid which deposited in the organs in large quantities was an hitherto unknown glucoside—a cerebro-glucoside. The important question arises at once: are compounds of this type deposited in all cases of Gaucher's disease, or are there two varieties of this lipoidosis, one characterized by cerebro-glucosides and the other by cerebro-galactosides? The many reports of the isolation of kerasin from Gaucher tissues appear to support the latter alternative, which, if proved to be correct, would be of considerable theoretical and perhaps of practical importance. However, in most instances, as already stated, the identification has rested mainly on physical properties which are probably not adequate, unless very carefully studied, to differentiate the cerebro-glucosides from the cerebro-galactosides. Lieb (14) and Mai (17) are the only investigators, as far as I have been able to find, who have attempted a direct identification of the sugar yielded by cerebrosides from Gaucher visceral organs. Both of these workers relied entirely on an examination of the osazone which, they found, had the melting point and crystal form of galactososone. Unfortunately the melting points of galactososone and glucososone are close together and they do not always crystallize in characteristic forms. Carbohydrate chemists do not regard the identification of an osazone as proof of the presence of a particular sugar without substantiating evidence. However, until more patients are studied with the

critical techniques used by Deuel and by Klenk the possibility must remain open that galactosides as well as glucosides are deposited in the visceral organs in different forms of Gaucher's disease.

Besides confirming Deuel's finding, Klenk made two other important observations. First, he showed that the cerebrosides of the brain, which, incidentally, were not appreciably elevated, were normal galactosides. Secondly, he showed that the cerebrosides isolated from the spleen of one of his patients contained palmitic, stearic, arachidic, behenic, and lignoceric acids, i.e., all of the saturated fatty acids with an even number of carbon atoms from C_{16} to C_{24}. Behenic acid with 22 carbon atoms was present in the largest amount. The same thing was probably true of the cerebrosides from spleen, liver, and lung of the other patient. This result stands in marked contrast to the fact that most of the fatty acids present in brain cerebrosides contain twenty-four carbon atoms. Thus the cerebrosides deposited in the visceral organs of these patients with Gaucher's disease differed from those of the brain, not only in the nature of the carbohydrate, but also of the fatty acids. These findings must be of far reaching significance in interpreting the underlying mechanism of Gaucher's disease.

Essential xanthomatosis. In the study of the xanthomatoses there has been no recent dramatic discovery such as those which have characterized other lipoidoses. Since Pinkus and Pick (18) in 1908 demonstrated the presence of doubly refracting cholesterol esters in xanthomata it has been pretty generally accepted that the lipid primarily involved, the lipid which is deposited in largest quantity in the tissues in this disease, is cholesterol. The evidence is twofold: first, analysis of xanthomata has usually shown a high content of cholesterol, and secondly, a marked hypercholesteremia is frequently present. I shall confine my discussion of xanthomatosis for the most part to these two points.

In Table III I have attempted to collect all of the cholesterol and total lipid analyses of xanthomata reported in the literature. Except for three determinations on xanthomata of the dura in Schüller-Christian disease, all of the analyses were carried out on tuberous xanthomata from the surface of the body (buttocks, hands, elbows, etc.). The data are of interest for several reasons. (a) Although in most of the determinations there was a definite accumulation of cholesterol, in some this was not the case. Wile, Eckstein, and Curtis (22) emphasized that in their patients the cholesterol content of the tumors was no higher than that of the surrounding tissues, but later Eckstein and Wile (23) reported the highest cholesterol concentration on record in a xanthoma from another patient. (b) In the majority of cases the cholesterol was predominantly in the combined form. (c) Xanthomata of the dura in Schüller-Christian disease gave analyses in the same range as the tuberous xanthomata of the skin and tendons. (d) Not only cholesterol but also the total lipids were usually present in high concentration, indicating that cholesterol is not the only lipid involved.

Biochemical interest in xanthomatosis has centered largely on the cholesterol of the blood serum. Thannhauser in his comprehensive monograph on the lipoidoses (28) divided the primary essential xanthomatoses into two types—hypercholesteremic and normocholesteremic—and recognized six sub-types in

the former and five in the latter category. In the hypercholesteremic class Thannhauser included the relatively common xanthelasma of the eyelids, xanthoma tuberosum, and tendon xanthoma, while in the group with normal serum cholesterol concentration he placed xanthoma disseminatum, the Schüller-Christian syndrome, and other conditions involving xanthomatosis of the bones, dura, brain, and other internal organs. As a biochemist, I am loath to criticize Thannhauser's attempt to systematize the classification of the xanthomatoses on the basis of a biochemical estimation, but unfortunately the data which he cited from his own records in support of this concept are not very convincing. Of eleven patients whom Thannhauser placed in the hypercholesteremic class, six had a concentration of cholesterol in the blood serum below 310 mg. per 100 cc.,

TABLE III

Cholesterol in xanthomata

AUTHORS*	CHOLESTEROL			TOTAL LIPID		REMARKS
	In fresh tissue	In dry tissue	Combined in total	In fresh tissue	In dry tissue	
	%	%	%	%	%	
Beeson, Albrecht (19)	1.8	6.6		16.8	61.1	
McWhorter, Weeks (20)	4.2					
Hermann, Nathan (21)	2.7, 2.2	5.8, 5.2	76			
Wile, Eckstein, Curtis (22)	1.5			8.9		
Wile, Eckstein, Curtis (22)	2.0			11.7		
Eckstein, Wile (23)	8.6			17.6		
Epstein, Lorenz (24)	5.1	18.6	82		44.7	†
Kleinmann (25)	4.3	15.8	84	10.7	38.8	†
Cowie, Magee (26)	3.5			7.0		†
van Bogaert, Scherer, Epstein (27)	5.1	16.2	2	11.5	36.5	
Thannhauser (28)	5.5		46	13.1		
Discherl (29)	3.7, 6.8		46, 21			
Sperry, Schick (30)	4.3	20.0	88			
Sperry, Schick (31)	5.0	14.5	76	11.5	33.7	

* Numbers in parentheses refer to the bibliography.

† Tumor of dura—Schüller-Christian disease.

including values of 210 and 216. All of these concentrations are well within the normal range which in the experience of Page, Kirk, Lewis, Thompson, and Van Slyke (32) and of myself (33), varies from a little over 100 to about 400 mg. per 100 cc. in adults. It may be that persons with concentrations in the upper part of this range have some latent pathology, perhaps a tendency to develop xanthomatosis, but the fact remains that a great many individuals with such large amounts of cholesterol in their blood are going about their daily work in apparently perfect health. It is possible, for reasons which I shall discuss later, that a particular concentration of cholesterol found in the serum of an individual is abnormal for that individual, even though it is within the normal range, but there is no way of knowing that unless the individual has been studied over long periods of time.

However, it is true that in most patients with xanthomatosis of the bones and internal organs and in Schüller-Christian disease, the serum cholesterol concentration has been found to be normal, frequently low normal, whereas the great majority of the many patients with xanthoma tuberosum and tendon xanthoma reported in the literature have manifested a definite hypercholesteremia. I have not encountered an exception in approximately ten patients whom I have had the opportunity of examining. On the basis of this evidence many investigators have concluded that the accumulation of cholesterol in the tissues in the latter types of xanthomatosis is the result of deposition from the blood stream, and, quite logically, they have treated the disease with a cholesterol-low diet in an attempt to reduce the cholesterol concentration of the serum. This approach has met with some success; Hermann and Nathan (21), Gaál (34), Thannhauser (35), and others observed a marked drop in serum cholesterol concentration on a cholesterol-low diet.

Perhaps the most thorough study of this sort was that of Schoenheimer (36) on a woman with typical xanthomata of the tendons and a serum cholesterol concentration of 852 mg. per 100 cc. Balance studies revealed that she was virtually unable to excrete cholesterol. Schoenheimer and his collaborators had shown (37) that the sterols of plants, which contain no cholesterol, are not absorbed by mammals, and it was easy, therefore, to administer a strictly cholesterol-free diet to this patient. Such a regimen had a decided effect: the cholesterol concentration of the serum fell from over 800 to around 300 mg. per 100 cc. in less than two months during which there was no appreciable excretion of cholesterol in the feces. The large amounts of cholesterol which disappeared from the serum (about 20 gm.) were in all probability not deposited in the tissues, since the patient felt much better on the cholesterol-free diet and since there was no increase in the size of the tumors; the cholesterol must have been destroyed. As evidence of this was an increase in the concentration in the serum of dihydrocholesterol, which Schoenheimer and his collaborators (38) had shown to be an end product of cholesterol metabolism. In summary, this patient was able to absorb but not to excrete cholesterol. On a general diet containing the usual amounts of cholesterol the process of degradation was not fast enough to keep up with the intake and cholesterol accumulated in the blood serum and in the tissues, just as it does in the rabbit receiving cholesterol, and for the same reason.

The hope that Schoenheimer's findings had solved the problem of hypercholesteremic xanthomatosis has unfortunately not been realized. Many patients do not respond at all to a cholesterol-free plant diet. A typical example is the case studied by Dr. Schick and me (30). The patient was an eleven year old boy with many xanthomata distributed more or less over the entire body and with a cholesterol level in the blood serum of about 800 to 900 mg. per 100 cc. He was placed on a diet consisting exclusively of foods of plant origin except for 500 cc. of cholesterol-free skimmed milk daily. This regimen, which was continued for a long time, had no appreciable effect on the serum cholesterol concentration or on the clinical course (Table IV). The same negative result was obtained in another patient whom I had the opportunity to study at the

Presbyterian Hospital, and this experience seems to be more common than that exemplified by Schoenheimer's case.

It appears evident that the underlying cause of the disturbance in the patient studied by Schick and me, and in many others who did not respond to a cholesterol-low diet, is not a failure in excretion of cholesterol; otherwise we should have obtained the same result that Schoenheimer did. There is another difference which may be of considerable significance. In Schoenheimer's patient before treatment with the plant diet the percentage of free cholesterol in the total cholesterol of the serum was very low: only about 6 per cent. The determination, which was carried out by the macro digitonin method, of which Schoenheimer was a master, must be accepted as authentic. My interest in this value arises from the fact that in several thousand determinations in patients

TABLE IV

Cholesterol content of blood serum of a patient (H. R.) with xanthomatosis

DATE	CHOLESTEROL		DATE	CHOLESTEROL	
	Total	Free in total		Total	Free in total
	mg. per 100 cc.	%		*mg. per 100 cc.*	%
4/18/34	810	27.7	6/18/34	765	29.3
4/21/34	869	27.4	6/22/34	815	29.6
4/24/34	685	29.5	7/ 3/34	795	28.6
4/27/34	845	27.8	7/10/34	772	29.3
4/30/34	850	27.6	10/ 2/34	853	29.0
5/ 3/34	948	27.8	5/18/35	762	27.4
5/ 4/34	Plant diet started		4/10/36	826	25.2
5/ 5/34	909	28.5	11/16/36	708	28.1
5/ 8/34	955	29.4	12/17/37	689	28.3
5/11/34	767	29.2	12/28/38	730	31.9
5/14/34	817	28.8	3/ 3/39	689	29.0
5/18/34	833	28.6	5/19/39	814	28.0
5/21/34	926	28.6	12/27/39	689	30.6
5/25/34	912	30.2	4/14/42	646	26.8
5/31/34	810	29.0			

with all sorts of diseases I have never seen so small a percentage of free cholesterol. Indeed in only a very few instances have I encountered values below the normal minimum of 24 per cent (33), and in most of these there was a probability that esterification of free cholesterol had occurred because the blood had been allowed to stand over long periods at room temperature before analysis (39). In all but three of the determinations carried out on our patient the percentage of free cholesterol in total cholesterol was within the narrow range found in healthy individuals: between 24 and 30 per cent (Table IV). In the three exceptions the percentage was slightly elevated; in none was it decreased. I have also found normal values for this percentage without exception in several other patients with xanthomatosis. It is a striking fact that despite the marked elevation of cholesterol in the serum of these patients the normal proportion between the free and combined cholesterol fractions was maintained.

There is another aspect of essential xanthomatosis which, though primarily a problem of genetics, is also of considerable biochemical interest. It is well established that the disease is hereditary; in fact there is strong evidence that all the lipoidoses are recessively inherited (40). In xanthomatosis this genetic factor may express itself in an apparent predisposition toward the disease as manifested by hypercholesteremia. The family of the patient studied by Schick and me will serve to exemplify this phenomenon. In 1934 the serum cholesterol concentration was 478 mg. per 100 cc. in the mother, 419 in the father, and 390 in a 9 year old brother. This high level has been maintained in the mother and brother as shown by analyses carried out about once a year since that time (Table V). (The father has not been studied further.) Another brother, aged 5, gave a normal value of 160 mg. per 100 cc. in 1934, but in 1937 this had in-

TABLE V

Cholesterol content of blood serum of relatives of a patient (H. R.) with xanthomatosis

SUBJECT	DATE	CHOLESTEROL		SUBJECT	DATE	CHOLESTEROL	
		Total	Free in total			Total	Free in total
		mg. per 100 cc.	%			*mg. per 100 cc.*	%
Mother	6/ 4/34	478	26.2	Brother (D. R.) (continued)	12/17/37	376	26.1
	10/ 2/34	410	26.8		12/28/38	381	29.7
	5 18/35	427	26.7		4/16/41	438	25.3
	11/16/36	444	26.4		4/ 7/42	576	25.5
	12 17/37	386	28.5	Brother (H. R.) aged 5 yrs.	6/ 4/34	160	25.6
	12/28/38	528	29.5		2/ 4/37	364	26.1
	4/16/41	460	27.0		12/17/37	278	25.2
	4/ 7/42	502	29.1		12/28/38	294	29.3
Father	6 18/34	419	28.4		4/16/41	353	25.5
Brother (D. R.) aged 9 yrs.	6/ 4/34	390	26.2		4/ 7/42	344	28.5
	2/ 4/37	477	25.6				

creased to 364. Subsequent determinations have ranged from 278 to 353 mg. of cholesterol per 100 cc. of serum, values which are probably well above normal for a boy of his age. Here we have an entire family—father, mother, and three sons—all with hypercholesteremia, but with only one member showing clinical manifestations of xanthomatosis.

Similar observations have been reported in a number of families. Bloom, Kaufman, and Stevens (41) recently reviewed this literature and added a striking example of their own. The parents of thirteen children were second cousins. Of nine of the siblings who survived infancy, five had severe xanthoma tuberosum of the hypercholesteremic type, and two of the remaining four had hypercholesteremia without any clinical abnormality. The father and most of eight half-siblings of the mother were also hypercholesteremic.

As pointed out by Bloom and his colleagues these findings suggest that "the

inheritable morbid factor may be constituted by a disturbance in cholesterol metabolism rather than by the cutaneous lesions." Some years ago I presented evidence (42) indicating that in each healthy individual there is a constitutional level of cholesterol in the blood serum which is maintained within a relatively narrow range of variation over long periods of time. Is it possible that the concentration of serum cholesterol is inherited and that the difference between normal families and those tainted with xanthomatosis is quantitative rather than qualitative?

Other lipoidoses. Jervis (40) called attention recently to the occurrence of neurocellular changes similar to those encountered in amaurotic idiocy, in gargoylism, infantile Gaucher's disease, and in a previously unknown condition of which he described six cases occurring in siblings of one family. This new disease resembled juvenile amaurotic idiocy and gargoylism in some respects but differed in essential details. Fractionation of the brain lipids in one of Jervis' cases gave an analysis almost identical with the average of Klenk's determinations in juvenile amaurotic idiocy. The protagon fraction yielded a strong Bial reaction indicating a high content of Klenk's Substance X. As far as I know, the only other biochemical study in these little known diseases is an analysis of spleen and liver in a case of infantile Gaucher's disease by Aballi and Kato (43). A fairly high content of cerebrosides (as kerasin) was reported, but the methods employed were not stated. There is much still to be learned about the biochemistry of the lipoidoses.

GENERAL DISCUSSION

Rowland (44) who was for many years the leading student of lipoidosis in this country, and many others with him, considered the lipoidoses to be a very closely related group of diseases. At the extreme some have believed that they are all variant forms of the same fundamental disturbance. There is little direct evidence for this point of view. On the contrary the lipoidoses differ among themselves in the type of lipids deposited, in the cells involved, in the clinical picture, and in other ways. However, the discussion of the various hypotheses which have been advanced to explain the mechanism of these diseases is facilitated by considering them as a group, and I am going to follow that course.

According to the most popular concept, in lipoidosis lipids are transported by the blood stream to the tissue cells where they are deposited. This hypothesis was suggested originally by the occurrence of hypercholesteremia in xanthomatosis, and in some cases, such as Schoenheimer's, it accounts very well for the deposition of cholesterol in the tissues. However, in many patients with xanthomatosis no elevation of serum cholesterol concentration has been observed. In these it is possible that hypercholesteremia had been present during the development of the disease and that the cholesterol concentration had returned to normal for unknown reasons before the first analysis was carried out; but this is highly unlikely in Schüller-Christian disease in which hypercholesteremia has rarely, if ever, been observed. In Niemann-Pick disease no increase in the concentration of sphingomyelin in the blood has been found (7, 8, 10).

It is clear from the foregoing evidence that lipoidosis may occur without any demonstrable increase in the concentration in the blood of the particular lipids which accumulate in the tissues. Conversely hypercholesteremia may be present for long periods of time, as in cretinism, without the occurrence of xanthomatosis. From these and other considerations Thannhauser (28) concluded that the lipids are formed in the cells where they are deposited as the result of an intracellular metabolic disturbance, and are not brought to the cells by the blood.

To account for the deposition of lipids in the absence of an elevation in the blood Bloch (45) and Schaaf (46) advanced the hypothesis that there is an abnormality in the proportion among the blood lipids in xanthomatosis with a resultant disturbance in the stable lipid emulsion, leading to the precipitation of one or all of the lipid constituents and deposition in the tissues. The evidence presented in support of this mechanism is not particularly convincing. Although considerable variations in the proportion among the lipid fractions of the serum were reported by these investigators in eight patients with xanthomatosis, no detailed determinations with the same methods in healthy persons were presented for comparison. The summarized normal values with which comparison was made included a range of total cholesterol concentration from 110 to 150 mg. per 100 cc. Actually, as I have said, the upper limit of normal for this constituent is much higher. Schaaf placed particular emphasis on abnormalities in the ratio between the cholesterol fractions in xanthomatosis as evidence for this hypothesis, but in several patients whom I have had the opportunity to examine the ratio was always within normal limits despite marked hypercholesteremia. Polano (47) found that the ratio of cholesterol to phospholipids in the serum was high in five of eight patients with xanthoma tuberosum, as compared with twenty normal subjects in whom the ratio was determined with the same methods. This result might be taken as offering partial support to the hypothesis of Bloch and Schaaf; however, Polano reported that in four of eight subjects with hypercholesteremia but without xanthomatosis the ratio was also elevated. Furthermore in twelve patients with xanthelasma of the eyelids no abnormalities in the proportion among the blood lipids were observed. Finally, as Thannhauser (28) pointed out, there is no evidence whatsoever that a disproportion of the lipids in the serum, even if it occurs in xanthomatosis, could lead to a flocculation of the colloid mixture and a precipitation in the tissues. Although the weight of evidence appears to be against the blood transport hypothesis, there are some arguments which support it.

(a) The inheritance of hypercholesteremia in families tainted with xanthoma tuberosum suggests strongly that an elevation in serum cholesterol concentration, or some underlying disturbance in metabolism leading to the hypercholesteremia, is the primary factor in this disease.

(b) The finding (42), to which I have referred, that each normal individual apparently maintains a serum cholesterol concentration within relatively narrow limits suggests the possibility, even though it may appear paradoxical, that a cholesterol concentration within the normal range may represent a hypercholes-

teremia. For example a cholesterol level of 300 mg. per 100 cc. might be normal for some individuals, but abnormal for a man whose constitutional level is 150 mg. per 100 cc.

(c) Kimmelstiel and Laas (48), and Christianson (49) injected cerebroside emulsions intravenously or intraperitoneally into mice and rabbits, and Dworacek and Pesta (50) placed finely divided kerasin in the peritoneal cavity of guinea pigs. Under each of these experimental techniques there developed a condition closely resembling Gaucher's disease in man. In similar experiments Beumer and Gruber (51) and Ferraro and Jervis (52) produced a picture simulating Niemann-Pick's disease by injecting intravenously a sphingomyelin emulsion into rabbits and one monkey. In all of these studies the changes found were limited to the visceral organs, especially the spleen; the brain was not involved. No chemical analyses of the organs were carried out, but the morphological picture resembled very closely, in some cases was indistinguishable from that seen in the spontaneous lipoidoses of man. Since in these experiments the lipids, which were presumably deposited in the tissues, must have been carried there by the blood, it is hardly necessary to point out that these findings offer considerable indirect support to the blood transport hypothesis. It is possible of course that the experimental changes found in the animals after lipid injections and the spontaneous lipoidoses of man are entirely different—they certainly are not identical; but at the least it may be concluded that conditions resembling very closely Gaucher's and Niemann-Pick's diseases may be produced in animals under conditions such that lipids deposited in tissues must have reached there via the blood stream.

(d) Finally, it must be pointed out that the absence of hyperlipemia does not disprove the blood transport hypothesis. The concentration of any lipid in the blood is a function of the rates at which it enters and leaves the circulation; if the rates are equal obviously no change in concentration will occur. It is quite possible that in lipoidosis without hyperlipemia the lipid removed from the blood and deposited in certain tissues is just equalled by an increased amount produced and added to the blood somewhere else. (In concluding that lipids are not transported by the blood to the cells where they are deposited in lipoidosis, Thannhauser (28) laid particular stress on Gaucher's disease because of the demonstration by Thannhauser, Benotti, and Reinstein (53) "that kerasin as well as the other cerebrosides are not normal constituents of the blood serum. They showed also that these cerebrosides were lacking in the serum in Gaucher's disease." The only statement on this point in the paper to which reference is made is: "We were, moreover, unable to isolate cerebrosides in quantities of serum as large as 1600 cc. (bovine)." On the other hand Kirk (54) reported the presence of considerable amounts of cerebroside in normal human plasma. Although the large variation in his data does not instill complete confidence in his findings, and although his method has been criticized by Thannhauser, et al. (53) and by others, it cannot be concluded from available evidence that no cerebroside is present in the blood and that, therefore, the blood transport hypothesis is impossible in Gaucher's disease.

While the failure to demonstrate an increased lipid concentration in the blood

of a patient with lipoidosis does not rule out the possibility that the lipids deposited in tissues were transported there by the blood, it may indicate that the primary lesion is in the cells where the deposition takes place, and is of such a nature as to cause the uptake of lipids from the serum by a sort of "vacuum" process. Under this concept decreased concentrations in the serum might be anticipated, and it is interesting that low values for cholesterol have been reported in Schüller-Christian disease. On the contrary in cases where there is hyperlipemia it is possible that deposition in the cells is a secondary process taking place as the result of the "pressure" of the increased concentration in the blood.

In summary, it cannot be decided on the basis of available evidence whether the lipids are formed in the cells where they accumulate, as Thannhauser believes, or whether they are brought there by the blood.

Whatever may be the physical mechanism by which the lipids are deposited in lipoidosis, in the ultimate analysis the accumulation must be the result of overproduction or underutilization, or of both, and it is of relatively little importance whether these abnormal processes are centered in the cells where deposition occurs or elsewhere in the body. The fundamental problem of lipoidosis is: what is the mechanism responsible for this overproduction or underutilization of lipids? In considering this question another arises at once: are the lipids which deposit normal constituents of the body or are they abnormal substances which are formed only in these diseases? As far as I know, this question has not been raised previously; it has been assumed that the lipids which accumulate are normal constituents. This is certainly true for cholesterol which is a well-defined compound; but the other lipid fractions are all mixtures of compounds having the same general structure, but differing in the fatty acids which they contain. It is possible, therefore, that the sphingomyelin, or cerebroside, or Substance X fraction which is deposited in lipoidosis is an abnormal mixture chemically, even though it has essentially the same physical properties as the normal lipid. The finding by Klenk (2) of almost pure stearyl sphingomyelin in a Niemann-Pick brain appears to be a case in point. More striking is the discovery by Deuel (16), confirmed and extended by Klenk (11), that the lipid deposited in the visceral organs in some cases of Gaucher's disease, differs from known cerebrosides both in the carbohydrate and fatty acid constituents. Until a lipid fraction of this composition has been identified in normal tissues it must be assumed that Gaucher's disease results from the production and deposition of abnormal lipids.

A few investigators have attempted to explain the underlying mechanism of overproduction or underutilization of lipids in the lipoidoses. The presence of lignoceryl sphingosine, a ceramide, in small amounts was shown by Fränkel and Bielschowsky (55) in pig liver, by Tropp and Wiedersheim (56) in beef spleen and lung, and by Schoenheimer (36) in the blood of his patient with xanthomatosis, the finding that ceramide is a normal constituent of the tissues, especially of those organs—spleen and liver—which are primarily involved in Gaucher's disease, suggested to Tropp and Wiedersheim that in this lipoidosis

the cerebroside which is deposited is formed through a combination of ceramide and carbohydrate. Thannhauser (28) amplified this hypothesis. He made the assumption that both sphingomyelins and cerebrosides are formed through combination of ceramide with choline phosphoric acid or carbohydrate under catalysis by the enzymes polydiaminophosphatase or cerebrosidase respectively. Thannhauser and Reichel (57) reported that cerebrosidase, which is practically inactive as it occurs in tissues, is activated by various compounds containing the sulphydryl group, whereas the same compounds inhibit the activity of the polydiaminophosphatase which splits phosphoric acid from sphingomyelin. On the basis of these findings Thannhauser (28) advanced the hypothesis expressed in the following sentence: "An unbalance of these two enzymes within the cells is assumed to be the underlying mechanism of Gaucher's disease on the one hand and Niemann-Pick disease on the other." As I understand it, according to this concept in Gaucher's disease cerebrosidase is activated while diaminophosphatase is inhibited, with the result that there is an overproduction of cerebroside in the reaction between ceramide and carbohydrate; in Niemann-Pick disease the reverse occurs with an overproduction of sphingomyelin in the reaction between ceramide and choline phosphoric acid. In other words the competition between two reactions for ceramide is thrown out of equilibrium in opposite directions in these two diseases. The only ceramide which has been isolated from tissues is lignoceryl sphingosine, whereas, as we have seen, several other fatty acids, especially behenic, are combined with sphingosine in the cerebrosides which accumulate in Gaucher's disease. The isolation of ceramides of this type from tissues and from sphingomyelin, if it could be accomplished, would strengthen this hypothesis.

Thannhauser stated further, "It has not been determined whether the synthesis of sphingomyelin is increased or the splitting of sphingomyelin is decreased within the cell." It is difficult to reconcile both of these possibilities with the concept I have just discussed or with the view that the lipids are formed in the cells where they accumulate. If the processes of anabolism and catabolism are both catalyzed by the same enzyme, then an overproduction of sphingomyelin in the cell as the result of activation of the enzyme is understandable, but an underutilization and resultant accumulation because of inactivation would involve the transportation of sphingomyelin to the cells by the blood.

Sobotka is the only investigator who has put forward a comprehensive hypothesis to explain the underlying mechanism of all the lipoidoses. Since Dr. Sobotka is a member of your staff, it would be presumptuous of me to attempt a detailed discussion of the ideas, and the evidence supporting those ideas, which he and his collaborators have presented in a series of papers (58–61). I shall confine myself, therefore, to a brief summary of this important contribution to the biochemistry of the lipoidoses. In general terms Sobotka's hypothesis states that in lipoidosis there is a deficiency of one or more of the various lipolytic enzymes which catalyse interconversions—exchange esterifications—among the different lipids. With that concept, considered in its broadest sense, I think no one can take serious issue. As I have already emphasized, either an

overproduction or an underutilization must be the cause of the accumulation of lipids in these diseases. Since these processes must involve chemical reactions, and since all reactions occurring in the animal body are catalysed, it is entirely reasonable and probable that an enzyme abnormality, either in the negative sense, as suggested by Sobotka, or perhaps in the positive sense, is responsible.

Sobotka based his hypothesis largely on two pieces of evidence. First, Sobotka, Epstein, and Lichtenstein (58) showed the virtual disappearance of neutral fat in a patient with Niemann-Pick disease. This they interpreted to mean that the normal conversion of other lipids to neutral fat by a process of exchange esterification had been blocked by a decreased activity of the enzyme systems which catalyse these reactions. Secondly, Sobotka, Glick, Reiner, and Tuchman (61) found a decrease in the methyl butyrate of the liver in several cases of lipoidosis. Freudenberg (62) was unable to confirm these findings in a pair of identical twins with Niemann-Pick disease. He found an increased amount of neutral fat in the blood and several esterases of various types in the liver with normal or even increased activity. Despite these contrary results of Freudenberg and the lack of much direct evidence in support of Sobotka's hypothesis, the general idea that abnormalities in the enzyme systems are responsible for the accumulation of lipids in the lipoidoses is the most reasonable explanation which has been offered.

I wish I could conclude with something more definite, but I think you will agree with me that on the basis of the evidence available no comprehensive picture can be drawn. As I said at the beginning of this lecture, the underlying mechanism of the lipoidoses remains a complete mystery.

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PERIODICITY IN ENDOCRINOPATHIC STATES

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The interest that Dr. Sachs has always shown in child neurology leads me to select from my history files three cases that for me have an unbounded fascination, in that they seem to portray an underlying mechanism in our constitution which controls the periodicity of occurrences in our life's history. The three cases are all children and I venture to present them because of Dr. Sachs' interest in children; and I hope that they may add,—perhaps a strange addition—to his long and wide experience in clinical medicine.

Not much has been written on the periodic occurrences of disturbance in the domain of the various internal glandular units. A notable exception has been the pituitary gland, whose function, many years ago, was usually associated with periodic changes in the organism. The ovarian menstrual changes, of course, it would be banal to describe. Their periodic occurrence is so much of a "natural" picture that practically no noteworthiness has attached itself to their comings and goings, and yet they are now considered as controlled in their periodic occurrence by the anterior pituitary. The thyroid gland also has its regular seasonal changes as well as its changes in concordance with the genital monthly flow. But there is a periodic wave that carries with it at its height, or perhaps at its greatest depth, a change in the resistance of the organism to various exogenous and endogenous factors. The facts of these changes of resistance are occasionally witnessed in an annoying symptomatology varying from an acidosis with allergic manifestations such as asthma, urticaria and eczematous skin eruptions, to real idiopathic epilepsy with characteristic attacks. With any of these, distinct pituitary migrainous attacks may likewise present themselves. It is as though the theory of Cannon of "homeostasis," that is to say, the state of equilibrium within us maintained by our various glandular mechanisms with their vegetative nervous system adherents, needs some qualification, in that there is apparently in this condition of "homeostasis," a lability, a "come and go," a surging and recession which disturbs this equilibrium in a regular and periodic fashion, undulatory in character. The distance between the waves is in each individual perhaps specific for him, while the height and depth of the wave may not be of sufficient value to cause critical changes in his homeostatic balance; and hence this theory of homeostatic variability can only rarely be applied,—and then, only because of their objectivity, the signs and symptoms can be witnessed and measured by the physician. How often the critical changes are subjective but not recognizable by the patient himself as simple variations in his well-being, one can only surmise; but undoubtedly many of the neuroses and psychoneuroses might be attributable to this undulatory basic periodic change in his homeostatic balance.

While many cases are seen that show indefinite correlations with this concept,

yet I am enabled to show three distinct cases, two of which are still under observation, one of them followed for about seventeen years, the other for six years in which the periodicity in the undulation was so pronounced that moderately accurate predictions of the next attack, sometimes months in advance, could be made. And this not only once, but during the entire course of the years of observation, without signal error. (That is to say, after the first year's observation during which the periodic recurrences were established.) The importance of knowing just when the wave was going to be at its lowest phase meant that in the intervals between lowest phases, *no treatment was necessary*, the entire simple treatment was carried out only for a few days during every periodic wave depression. In two cases this was only once in two months! Before we had succeeded in establishing the periodicity, the sudden occurrence of an attack of urticaria with asthma was blamed upon some adventitious cause, some indiscretion of diet, over-exercise, pollen and what-not. And in one case—a girl—these attacks occurred as early as the second year of life and hence the gonads were unsuspected. Another case—a boy—also in his second or third year, would come down with high temperature, 104°F., with acidosis, eczema, diarrhea and prostration, out of a clear sky. Again, all kinds of causes were found—enlarged tonsils, phimosis, sinus infection and the usual diet suspicions. The third case, that of a young man with the symptomatology of idiopathic epilepsy with migraine was followed only for a comparatively short time, but long enough to establish periodicity in the attacks. He left our observation because of our advice to take no medication whatever until we were certain of our ground. This seemed to him and his parents an unpardonable waste of time.

Of course, all of us who deal with young women that suffer from any endocrinopathy whatever, find that the disturbance is modified for better or worse at either menstrual periods or at ovulation time. Therefore the three cases herewith presented are of special interest for two of them are boys and the third is a girl of two to three years of age whose menstrual periods began only in her thirteenth year.

A short history of each case, covering the salient points, is herewith appended.

CASE REPORTS

Case 1. Child, girl, one and one-half years of age, was sent to me by Dr. D. L. B. of New York because of her growth disproportion, the legs being much too short for the thorax. The torso-leg ratio in the child was 25:35 (Numerator: distance from sterno-clavicular junction to anterior superior spine. Denominator: anterior superior spine to external malleolus of ankle: this fraction should be approximately one-half). The highlights embodying only the salient features are as follows: She was chubby, with fat thighs and rather massive calves, and her fingers were quite markedly fat. There were fatty pads at the knee and elbow joints and some genu-valgus. She was moderately healthy with occasional attacks of acidosis with temperature, vomiting and asthma. Blood examination disclosed a mild anemia with 4,100,000 red blood cells, 78 per cent hemoglobin, 7000 white blood cells, 35 per cent polymorphonuclear leucocytes and a coagulation time of 8 minutes. X-ray examination of the chest showed a large thymus gland, and of the skull a diminution of the calcium in the vault and a pituitary fossa quite small, and completely bridged over by a broad and sharply defined bony roof. A diagnosis of hypocalcemia, hypopituitarism and

enlarged thymus was made and she was placed on treatment to cover these conditions: that is to say, calcium, cod liver oil, pituitary substance (both anterior and posterior) and small doses of thyroid; with x-ray treatment of the thymus. Without entering into too much detail, at the end of five years the patient had improved considerably. The thymic shadow was much narrower, she had grown 12½ inches in four years, chiefly in the extremities so that her torso-leg ratio was now 290:575, approximately normal. She was much more alert, her various fatty pads and prominences were much reduced and in every respect she seemed fairly normal, except that from time to time she would have days of great fatigability, with occasional eczema and acidosis. No notation had been made as to the dates of these occurrences. All medication was discontinued excepting the calcium which was given irregularly. The x-ray examination of the head showed a slightly larger pituitary fossa, still completely roofed in. The hemoglobin and red blood cells were occasionally deficient. She complained of early morning fatigue especially, and needed much rest in bed to overcome it. She showed a slight cardiac arrhythmia.

Then, on November 13, 1929, she developed a severe cold with acidosis needing glucose irrigations: recovery followed speedily; no medication was necessary after the recovery.

I saw the patient again in January 1931. She had had some attacks of acidosis (a bad one on November 22, 1930) for which glucose irrigations were again advised. Some anemia, and some myotatic irritability were present. Viosterol was added to her iron treatment. She was taken to France for special "hay fever" treatment, with apparently good results. In the autumn of 1931 she underwent an appendectomy satisfactorily. During the winters of 1931–1932 and 1932–1933 she did remarkably well with the excepton of her acidosis attacks. These occurred as follows: November 22, 1931; January 23, 1932; March 22, 1932; May 23, 1932; July 18, 1932; September 6, 1932; October 30, 1932; December 19, 1932; February 17, 1933; April 10, 1933; July 7, 1933; and August 31, 1933.

With the acidosis attacks there was sneezing, asthma, cough and temperature, together with purpuric eruption on hands or legs. The intervals, i. e., days between the successive dates of the attacks, are as follows: 62, 59, 62, 56, 50, 54, 50, 50, 54, 58, 55.

We now, on the basis of this approximate periodicity, gave her no medication until five days before the next attack was due and continued it for eight to ten days, which would allow for discrepancy in the calculation. This treatment consisted in giving calcium lactate, bicarbonate of soda, small doses of thyroid (grain one-tenth) and pituitary substance (anterior lobe, grains two; whole gland, grain one-sixth). Cod liver oil and viosterol and ovoferrin were included. As a result, or perhaps one should say, *following* this regimen, during the remainder of 1933 and the entire year 1934 we had the following data.

September 30, 1933: very bad bronchitis for three weeks (adventitious?).

November 17, 1933: asthma and nose bleed for two days. Then, after 99 days, on

February 24, 1934: slight nose bleed and asthma, followed in 56 days, on

April 20, 1934: sick with asthma for three days.

September 7, 1934: attack of vomiting, diarrhea, mucous colitis, etc.

And no further upsets until January 28, 1935, with severe asthma. Again May 17, she had asthma and German measles—an interval of 109 days or about double the periodic occurrence of 54 days. Again came a clear epoch of about six months to December 29, 1935, with a mild attack of asthma lasting only one day; this interval representing four periods of 56 days each! Then followed a regular occurrence again of asthma, migraine and nose bleed on January 28, 1936; February 28, 1936; March 20, 1936; May 22, 1936; August 27, 1936—nausea and asthma.

The reason for this change in the periodicity was seen on September 27, 1936, for then the first menstrual period occurred, at the age of 13 and ⅓ years. During the past year, 1936, the pubic hair had increased markedly, the breasts had developed and general features of maturity had supervened. During 1937 there were only two episodes of asthma and hay fever. In the following two years no attacks whatever were recorded. Then a bad attack occurring from October 6 to October 14, 1940, and quite severe, kept her in bed. Interestingly, just 57 days after this attack ended, namely, on December 10, 1940, she acquired

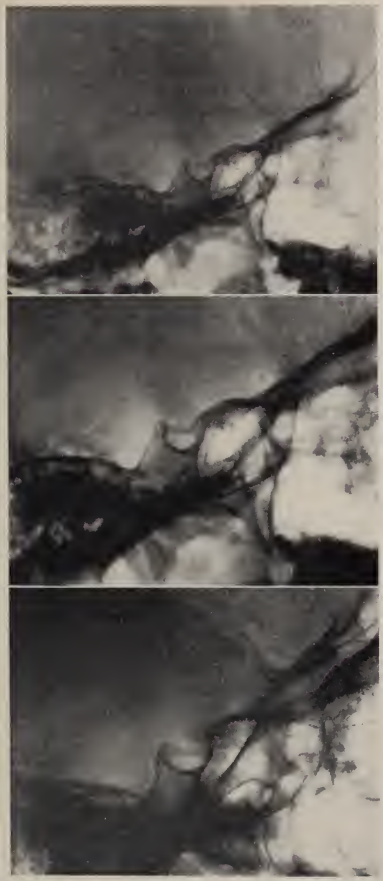

FIG. 1

FIG. 2

FIG. 3

These three successive photographs represent the sella turcica of Case 1. The child began life as a thymic, hypopituitary type of case with periodic homeostatic disturbances.

FIG. 1. At the age of about three years.

FIG. 2. At the age of nine years.

FIG. 3. At the age of eighteen years, showing a gradually enlarging pituitary cavity, but with distinct bridging in all three photographs.

a curious type of pneumonia which for want of a better description was called a virus pneumonia, with a temperature of 103°F., which did not respond to the usual sulfapyridine or sulfathiazole treatment, but which she successfully combated. Since that time she has done exceedingly well, no further asthma or acidosis; occasionally migraine only; menses regular and uneventful. Some complaint of lack of initiative, and mild sluggishness, different from her usual self. The x-ray examination of her sella tureica taken in 1941 after a lapse of nine years shows the same roof of the cavity as before, but the cavity itself has increased in size as can be seen by the accompanying photographs (figs. 1, 2, 3).

Here we might add that in 1932 her visual fields showed a rather marked contraction on both sides which later disappeared, so that now they appear normal.

Comment. We have a history in a child, beginning in the second year of her life, characterized by distinct pituitary, thymic and calcium disturbances and showing growth abnormalities and attacks of presumably allergic character, consisting largely of skin eruption, asthma, gastro-intestinal upsets with temperature. The history, as given, recorded these attacks as irregular in their appearance and usually, though not always, produced by indiscretions in diet; occasionally they seemed to come out of the blue. As soon as these attacks were ordered recorded on the calendar, a curious relationship was established. They came at intervals of approximately fifty to sixty days and could be foreseen, and treatment was given only when they were expected. This treatment ameliorated them considerably so that at times the interval lengthened from four to six months. Her health in all respects remained quite good with the exception of a mild anemia. Then, she began to develop and mature so that her breasts became prominent and her pubic hair increased. Now a new series of events were ushered in at her thirteenth year. She began to have attacks of migraine, nose-bleed, with occasional mild asthma, these attacks coming on with almost menstrual regularity, and eventuated in her first menstrual period in September 1936. Since then, her menstrual periods have been quite regular, her "allergic" attacks have all but disappeared: no treatment except for a mild anemia has been carried out and occasional doses of calcium and viosterol were given. One curious set-back occurred in 1940: bad hay-fever with asthma lasting one week; and fifty-seven days thereafter a sudden attack of what was called "virus pneumonia" laid her low, from which she recovered excellently. Thus we see that a curious periodicity, apart from any apparent exogenous factor, took place in her endogenous mechanisms, lowering her power of resistance, and diminishing her ability to maintain her life at normal levels. Possibly the pituitary gland was responsible among her internal factors for this regular disturbance. The reason for this assumption is that during one summer from April to September, no upsets occurred and the usual summer dates in other years were marked by much milder attacks. We now know that sunlight has marked influence on pituitary activity. This pituitary activity would most certainly be co-effective with the sympatho-adrenal system which Cannon believes, and we with him, controls and presumes a homeostatic condition in the internal environment. Claude Bernard is authority for the statement that this internal environment has developed as the organism has developed; and with it there have been evolved *remarkable physiologic devices* which operate to keep it

constant. And Zinsser adds to this that "the individual differences in resistance to disease displayed so plainly by the human being are often due to some fortuitous factors as metabolic fluctuations." And may we add to this that these metabolic fluctuations are at times, if not always, *periodic* in their vagaries. Then if such periodic fluctuations can be charted, we will be enabled to forecast the future ups and downs which modify our patients' reaction to environment both endogenous and exogenous.

Case 2. The second case which is of interest belongs to the same category as the one already cited, except for the important fact that this case is that of a *boy*. At the age of two years this patient began to have "allergic" attacks consisting of fever, nausea and vomiting, asthma, eczema, or urticaria and general malaise with acidosis. His condition at times seemed quite critical and various exogenous factors were usually found to have been operative preceding each attack—such as exposure to the pollen in the garden, occasionally milk and eggs and oatmeal. But then at times the attack seemed to come without apparent cause. And furthermore at odd times he was able to take oatmeal or eggs without an attack. The mother, quite intelligent, would explain these vagaries by stating that his "health seemed particularly good" at these times. When I was called in to see the child the outstanding physical signs were those of a low calcium utilization character—myotatic irritability, myoedema and a bilateral Chvostek reflex. The child was placed on a treatment of cod liver oil and calcium and did fairly well, though from time to time the allergic manifestations came on. These were irregular in their appearance and seemed to follow no particular course. My experience with the first case at once came to my mind and the mother was ordered to prepare a calendar of events in the boy's life such as exposure, suspicious foods, overexertion, sleeplessness and so on. Of course the dates of any attacks were to be noted also. The resulting chart after a few months showed a number of incriminating factors appearing at various and apparently unrelated times. But one rather interesting series of occurrences maintained a periodicity, which, if I had not had previous experience, might have been overlooked. In short, no matter how involved and overlapping the various factors appeared, two attacks of "allergy" with acidosis occurred at 56 days interval. Thereafter, every fifty-sixth day with a few days before and after was set as a possible critical period and intensive treatment was ordered just previous to this time. For a year or so, the attacks would come on at the expected time but in milder degree. Then an occasional lapse was noted, but the succeeding attack would appear at twice the fifty-sixth day interval, namely, about 112 days. This went on for two years, after which no further attack occurred and no further observations were made. Then again, because perhaps of a let-down in the treatment, two attacks occurred at the usual 56 day interval. And there the history stops. At present, the boy is about eight years of age, is fine and intelligent, developing well and no illnesses or allergic attacks have been manifest since.

Comment. In this case again, the period was the equivalent of two menstrual ones. One may theorize as to the reason for this on the basis perhaps of an effeminate male child with breast formation and reversive type of genitals, but this is certainly not the case of the boy under observation, who is distinctly male of pronounced masculine build. It leads me to suspect that periodicity of disturbed function in humans, whether menstrual or "allergic" or "psychobiologic" may be due to some lack of concordance of the internal mechanism as a whole with the perturbations of some of its parts, a sort of astronomical set-up! And these perturbations bring about the various undulatory phases of "homeostasis."

Case 3. The third case is that of a young man fifteen years of age with headaches combined with visual disturbances, scotomata, involving changes in the color scheme of objects. During the attacks he becomes dyspneic, nauseated and feels he cannot walk; the visual disturbance precedes the headache. The attacks last about a day. He neither falls nor has any convulsive seizures in the attacks. Subjectively it was interesting to learn that the boy thought that he had a brain tumor for he felt at times as though there were a distinct mass at the base of his skull and within it, which exerted intense internal pressure with resultant visual and migrainous symptoms. Between attacks the pressure was relieved. His examination disclosed a boy 5 feet $7\frac{3}{4}$ inches in height, weighing $144\frac{1}{2}$ pounds (he had formerly been very fat) with rather marked general hyperextension. About the hips were lineae atrophicae quite white; the scrotum was of the recessive character, entirely surrounding the base of the penis, the testicles were small, the right one not entirely descended and there was still some undue fatty distribution around the girdle and hips. Blood pressure and pulse were normal; heart normal; the fundi of both eyes were normal, confirmed by an ophthalmologist; and all reflexes were within normal limits. There was no Babinski

FIG. 4. This photograph shows a rather large sella turcica, facetted and squared off at the base (a frequent finding in certain types of migraine): in a case of periodic disturbances of the homeostatic balance.

sign or even a *signe d'eventail.* The laboratory reports were quite normal except that the non-protein nitrogen of the blood was rather high, 31 mg. for 100 cc. of blood. The blood count and hemoglobin were normal. Basal metabolic rate was minus sixteen per cent. Of interest was the fact that his blood contained only 9.4 international units of male hormone instead of 15 to 24 I. U. per 24 hours, and furthermore that the x-ray examination of the skull showed the sella turcica to be quite large and squared off. Its appearance is indicated by the accompanying photograph (fig. 4), resembling the facetted sella which I have frequently described as a finding in migraine.

Of moment in the present discussion was the fact that although he stated that his attacks came on at quite irregular times, when his record, which he had kept on a calendar, was studied, the following dates appeared as days of attacks: June 20; 57 day interval—August 26; 61 day interval—October 26; 57 day interval—December 22; 57 day interval—February 17.

Again about a double menstrual interval between attacks. In this case because of his low male hormone content, a soft undescended testicle and some reversive characteristics of his scrotum, one might conceive of other feminine characteristics one of which would be

the periodic occurrences of internal glandular perturbation involving the pituitary and the gonads particularly. But in this as in the other cases the queer recurrences at 57 to 61 day intervals gives rise to the suspicion that there is a recurrent phase of a failing homeostatic principle involved. Because of the fact that this boy had a low basal metabolic rate, we took him off all his previous medication which had consisted in various gonadal and gonadotropic preparations and placed him on a very small thyroid dose in order that the attacks might be followed for a few months uninfluenced by other glandular medication. We witnessed one attack, that of February 17, and because the boy's mother thought that the condition was one of epilepsy she decided to take the boy to a *neurologist*!

Comment. And so, we have three distinct cases involving a periodic series of so-called "allergic" attacks—the attacks occasionally being referred to indiscretion in diet, pollen, food idiosyncrasies, fatigue, excitement and often apparently quite causeless. When the occurrences were scheduled, it was found that a certain periodic relationship existed between their appearances no matter what the cause or lack of cause. And curiously, these periodic intervals were almost of the same duration in all three cases, although the individuals represented by them were quite different in age and sex and character. And the symptoms were usually those involved in a breakdown of the alkaline reserve of the body—the "*fluid matrix*," as described by Cannon,—which collapse occasioned the signs and symptoms of an adreno-pituitary-sympathetic syndrome—acidosis, asthma, dyspnea, urticaria, fatigue, migraine and gastro-intestinal disturbances. It seems to me that the rationale of the entire symptomatology can be understood by assuming an undulatory mechanism involved in "homeostasis" with a certain wave-length of days or weeks, with the usual crest and depth of any undulation—the depths representing the lowest period of resistance and the crest the highest of the individual. Why the wave length (or its multiple) should be alike in all these cases and what determines it is a biological problem of no mean character. Also it must be remembered that the wave is subjected often to cross-waves of other periodicity and character, often changing by such interference, the height of the original undulations. And an example of this can be seen in the first case during the year preceding the onset of menstruation. Here the equivalent dates at times correspond with the original undulations and at times occurred independently so that our calendar was much complicated. Are we not constituted individually as a sort of astronomical system with parallel and conflicting orbits, with attractions and repulsions, and with an occasional comet throwing everything out of gear?

BONE BLOCK FOR PARALYTIC AND SPASTIC EQUINUS

A Study of End Results of 100 Cases (1925–1940)

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In planning my contribution to the Bernard Sachs Anniversary Volume, it seemed to me most fitting to contribute something related to one of his great interests—Child Neurology. Before 1923, drop foot was treated by braces and spastic equinus by tenotomy. The latter often had to be repeated and many times ended in a crippling reverse deformity, calcaneus. The original operation designed by Campbell in 1923 was modified in 1925 by me, and now is the standard technique for drop foot and spastic equinus as used at the Hospital for Ruptured and Crippled.

This report is confined to a study of one hundred cases covering a period of fifteen years, in which the modified bone block of Campbell has been used. It has yielded most gratifying results. None of the cases has been under eleven years of age, but the age which is considered best for the operation is beyond fourteen years, when the bones of the foot have attained their normal growth. The cases were instances of a definite foot drop, associated with an active calf-muscle group and at times with slight power in the tibialis posticus. The etiology in a great number of cases was anterior poliomyelitis, but there were many cases of spastic equinus due to hemiplegia of a congenital origin, lethargic encephalitis or fractures of the spine. The flaccid paralyses due to traumatic division of the common peroneal nerve were also included. Most of the cases were associated with a marked varus deformity of the foot which needed operative correction by wedge resection on the outer border of the foot. The operations were performed at the Hospital for Ruptured and Crippled.

In a number of our earlier cases, in following the Campbell technique, a stiff ankle resulted and the only motion was in the mid-tarsal joints which caused an awkward gait or heel-walking. Fractures of the tip of the transplanted bone often occurred, accompanied by no symptoms, but often followed by increased motion in the joint. At times we were obliged to excise the redundant tip to secure motion in the ankle or to correct secondary varus deformity.

Upon excision of the tip of the transplanted bone of the posterior surface of the tibia, the satisfactory result was evident with an increased range of motion. It seemed that very little impingement of the bone was necessary to obtain the desired result. We have all noted how a small displaced osteochondral fragment in the knee joint or elbow joint may limit motion. By using the same principal in elongating the posterior surface of the astragalus, a normal joint surface can be secured and drop-foot satisfactorily prevented and with a considerable range of motion.

The operation is performed with the use of a tourniquet. The first step in the operative technique is the excision of the calcaneo-cuboid articulation and

the correction of the varus and placing of the forefoot in abduction. The posterior ankle joint is then exposed through a small incision lateral to the Achilles tendon; the tendon is then divided as in Campbell's original description. The deeper structures are reflected lateral from the midline and the ankle joint proper is entered. The projecting portion of the astragalus is excised with a curved

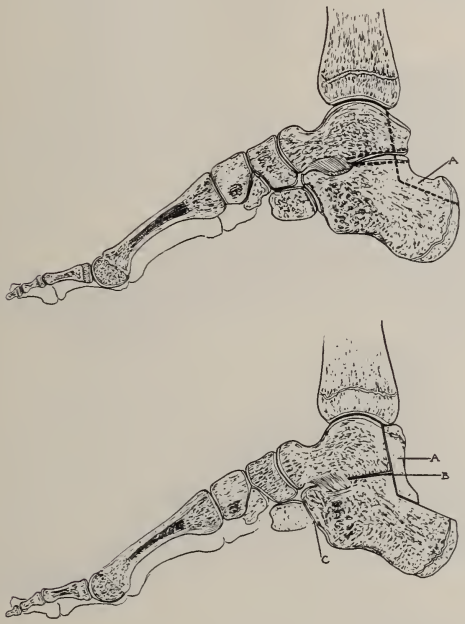

FIG. 1. Showing excision of tip of astragalus and subastragaloid joint with removal of graft from superior surface of os calcis. The lower picture shows bone block impinging against lower surface of tibia.

flat chisel (fig. 1) and the subastragaloid joint is destroyed, taking a large wedge from the outer side of the articulation so that the posterior part of the foot can easily be placed in valgus. A large section of the os calcis measuring $3 \times 2 \times 1$ cm. is reflected, shaped and fitted under the posterior aspect of the tibia with the denuded surface of the transplanted bone resting against the astragalus. The transplanted bone must fit accurately and touch the inferior surface of the tibia

only when the foot is in ten degrees of plantar flexion. The transplanted bone should remain in place without fixation, if it is cut properly. The deeper tissues are then closed with interrupted sutures over the posterior articulation of the ankle joint. The tendo-Achilles is repaired with elongation. A plaster-of-Paris dressing is applied with the foot at right angles to the leg and in valgus and the forefoot in slight abduction. Walking is begun in plaster at the end of one month and the plaster-of-Paris dressing is entirely removed at the end of the third month. The outer border of the shoe, heel and sole, is raised one-eighth

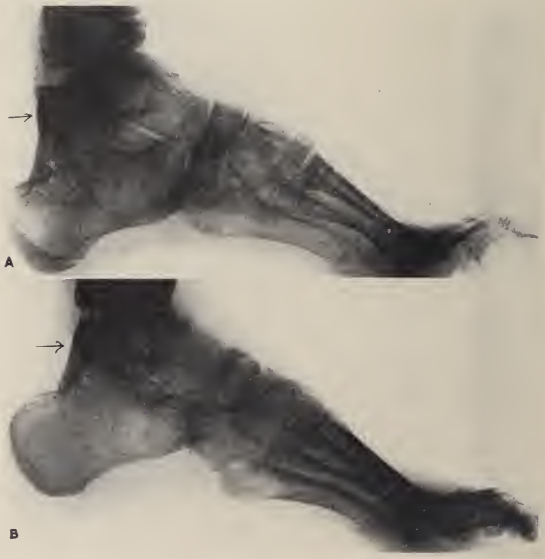

Fig. 2. (A) X-ray appearance of bone block ten years after operation. (B) X-ray of another patient twelve years after operation.

of an inch to retain the valgus position of the foot and walking is allowed without support. The elevation of the shoe is continued for one year, after which time any type of shoe is satisfactory, without alteration.

The classification of the end results of one hundred cases done (1925–1940) by the modified bone block procedure was as follows:

Anterior poliomyelitis was the proved etiology in sixty cases of paralytic equinus; four cases were due to traumatic division of the common peroneal nerve. The cases of spastic equinus were divided as to etiology: twenty-six spastic hemiplegia or paraplegia, congenital; seven the sequelae of a fractured spine; and three due to the remains of lethargic encephalitis.

Varus deformities occurred in eight cases and were necessarily corrected by wedge resection of the calcaneo-cuboid joint. The occurrence of this deformity was explained by an active tibialis posticus muscle. Because of this fact, the routine resection of the calcaneo-cuboid articulation was practiced, as well as a

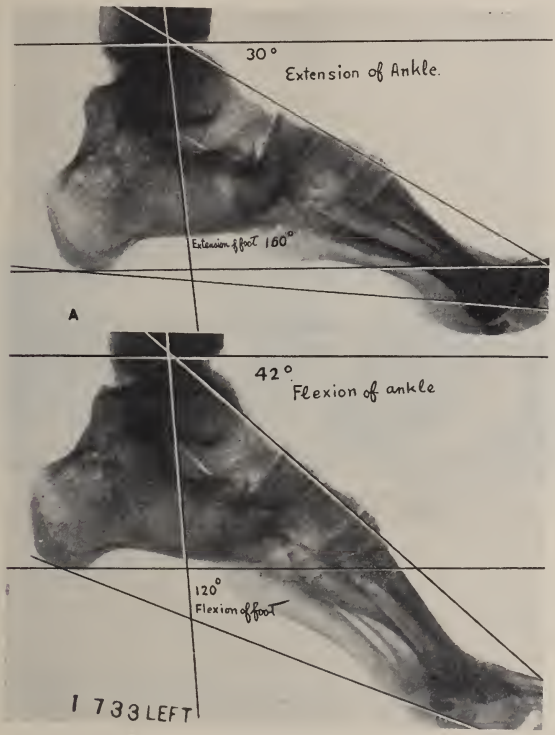

Fig. 3. (A) and (B) Showing the range of motion following bone block operation: 12° in ankle proper and 20° in forefoot, making total range of 32° of motion in postoperative foot (about half of normal).

resection of a portion of an active tibialis posticus tendon. The varus deformity was not noted in my later cases.

Six patients of the poliomyelitis series required transplantation of a weak peroneus longus to the mid-portion of the foot because of too much valgus.

The cases which showed the most satisfactory walking gait were those in

which the range of dorsiflexion was the greatest and was produced by considerable elongation of the Achilles tendon.

The operations performed for spastic equinus have prevented the recurrence of the equinus with marked diminution of spastic tendencies. I am not prepared to explain the loss of spasticity.

One operation performed a year after plastic repair of the common peroneal nerve was found to have secured the return of function to the nerve but the bone block was not removed as the patient was satisfied.

Of the total number, there were eight bilateral cases, and the only death which occurred in this group (a case of bilateral spastic equinus due to the after-effects of lethargic encephalitis) occurred immediately after operation.

In twenty of the cases there was slight difficulty in healing of the posterior incision, but within one to three months satisfactory scars resulted. There were no infections of the transplanted bones or joint surfaces.

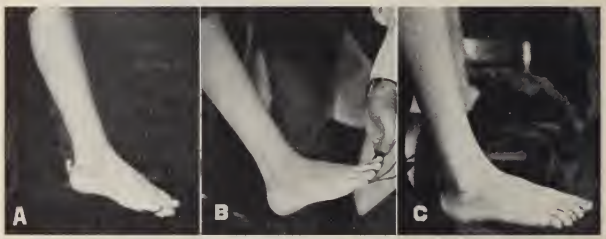

FIG. 4. (A) Extent of paralytic equinus in patient suffering from poliomyelitis. (B) Limit of dorsiflexion in same patient. (C) Same foot following bone block operation with equinus checked at 115°.

Only one case required revision of the height of the transplanted segment of os calcis in order to allow more plantar flexion. The operation should not be performed before the age of twelve because of growth and the possibility of bone absorption.

CLASSIFICATION OF CASES

One hundred operations. Eight bilateral (1925–1940).

ETIOLOGY

Sixty paralytic equinus, poliomyelitis; 4 paralytic equinus, traumatic division of common peroneal nerve; 26 spastic equinus, hemiplegia or paraplegia; 7 spastic equinus, fractured spine; 3 spastic equinus, lethargic encephalitis.

COMPLICATIONS

Eight varus deformities, due to overactive tibialis posticus muscle required secondary wedge osteotomy and resection of tibialis posticus tendon. As

a preventative, all active tibialis posticus tendons were resected at time of bone block.

One revision of height of transplanted bone to allow more extension of foot.

One death, bilateral spastic equinus due to encephalitis.

Twenty difficulty in healing of posterior wound, all healed within three months.

SUMMARY

An operative procedure, used in one hundred cases, consisting of a modification of the classical posterior bone block of Campbell is presented.

It consists of an excision of the calcaneo-cuboid articulation, to prevent adduction and varus deformity of the forefoot; a posterior subastragaloid arthrodesis with a constructed anatomical elongation of the posterior aspect of the astragalus produced by a reflected segment of the os calcis, which articulates with the inferior posterior surface of the tibia. The degree of plantar flexion can be accurately controlled by the height of the reflected transplanted segment of the os calcis.

The final result is a foot in the attitude of weakness (valgus) and blocked in plantar flexion at an angle of not more than 105° which relieves the equinus, thus securing an extremity which is stable, painless and with 10° to 15° of motion in the ankle joint proper. Walking then can be executed with grace and ease.

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REFLEXES OF THE ABDOMINAL AND PLANTAR MUSCLES[1]

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Among the numerous reflexive phenomena, two categories are particularly important in routine neurologic examinations: the deep muscle reflexes and the superficial muscle reflexes. The deep reflexes are also designated as tendon reflexes, periosteal reflexes, etc.; Hoffmann calls them *Eigenreflexe*. The superficial reflexes are also called skin reflexes, termed by Hoffmann, *Fremdreflexe*. The deep reflexes are essentially muscle-stretch reflexes in which the muscle reacts to brisk stretching with brisk contraction. This property may be regarded as common to all striated muscles.

For proper evaluation of the reflex phenomena observed on clinical examination, it must be understood that the visible and palpable contraction of a muscle on stretching varies greatly according to its function and especially according to its position and accessibility to passive stretching. In some muscles the contraction on stretching is not easily demonstrable or it exists only in latent form. Thus, in persons with normal pyramidal tracts, the intensity of the deep reflexes may vary markedly. The reflexes either may be greatly exaggerated or they may be so weak that they are hardly noticeable or not demonstrable at all. In a normal person many a reflex may be seen only when there is a general, purely functional reflex hyperirritability.

It is a universally accepted law that in the areas affected by a pyramidal tract lesion the deep reflexes are exaggerated while the superficial reflexes are diminished or lost. For clinical purposes it is essential to stress that in the areas affected by a pyramidal tract lesion, those deep reflexes which normally are very weak or hardly perceptible become distinct while those which normally are not perceptible at all become apparent. Thus, a pyramidal tract lesion exaggerates the existing deep reflexes and makes the latent ones visible. Interesting and diagnostically important conclusions may be drawn when these general principles are applied to the reflexes of the abdominal and the plantar muscles.

Since Rosenbach first described the abdominal reflexes and Strümpell pointed out their early disappearance in multiple sclerosis, the testing for these reflexes has become a part of even a superficial routine neurologic examination. The abdominal reflex is a classical representative of a superficial reflex; upon stimulation of the skin of the abdominal wall the muscles contract. The disappearance of the abdominal reflexes in a pyramidal tract lesion constitutes a very important and universally recognized sign of pyramidal tract affliction. Text books speak of these reflexes as superficial or skin reflexes. But from a purely theoretical standpoint it would appear justifiable to assume that the abdominal muscles should also have deep or muscle stretch reflexes. This assumption is indeed correct. The abdominal muscles, like all others, react to sudden stretching with

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contraction. Because of their expanse and their unusual length from origin to insertion, stretching of the abdominal muscles in order to evoke their contraction may be brought about by different methods and at various points. The muscles may be stretched directly by tapping the hand, a ruler or a tongue blade placed on the abdomen, or indirectly by tapping the bones near the origin or the insertion of the muscles. All these methods result in visible and palpable contraction of the abdominal muscles.

Many scattered observations on reflexive phenomena have been reported under different names in the literature, all of them representing merely the same abdominal muscle reflex evoked by stretching (Forster, 1908; Guillain and Alajouanine, 1923; Troemner, 1923; Monrad-Krohn, 1925; Galant, 1926; Trioumphoff, 1927; Dosužkov and Bodlák, 1929; Rabinovitch, 1935; Weingrow, 1936; and Nielsen, 1941). However, a clear exposition of these phenomena has never been made in text books and knowledge of their existence has not gained deserved recognition among neurologists. Furthermore, the relationship of the abdominal skin reflexes to the abdominal muscle reflexes and the enormous diagnostic importance of the latter has not been stressed sufficiently, except perhaps by Troemner. This diagnostic importance may be seen in the following summary of the possible behavior of both types of reflexes:

1) In normal condition—abdominal skin reflexes are present; abdominal muscle reflexes are present, hardly noticeable, or absent.
2) In a lesion of the pyramidal tract above the sixth thoracic segment abdominal skin reflexes are absent; abdominal muscle reflexes are exaggerated.
3) In a lesion involving the lower part of the thoracic spinal cord—abdominal skin reflexes are lost; abdominal muscle reflexes are lost.

From many years experience it can be stated definitely that the careful observation of the two types of reflexes has proved a valuable adjunct to neurologic diagnosis. In some cases it has been a decisive element in the diagnosis.

The plantar muscles, the plantar flexors of the toes, behave exactly as the abdominal muscles. They have a superficial, or skin reflex which is generally known as the plantar reflex. It consists of flexion of all the toes on stroking the skin on the plantar surface. This reflex is positive normally but is lost in a pyramidal tract lesion. Reference may be made here to the so-called "dumb sole," when stroking of the sole does not result in flexion of the toes, the phenomenon which may constitute a precursor of the classical sign of Babinski. However, we are not concerned here with the Babinski sign since it does not belong strictly to the category of reflexes under discussion and since it is not a reflex of the plantar muscles but of the dorsiflexors of the toe. It is justifiable to assume, from a purely theoretical standpoint, that, like the abdominal muscles, the plantar muscles have also a deep reflex consisting of contraction of the muscles with flexion of the toes on sudden stretching. This deep reflex of the plantar muscles is clinically not easily, if at all, perceptible, apparently because these muscles are situated deeply and their relationship to the toes is mechanically such that in normal persons their tone is not sufficient to produce a visible reflexive contraction on stretching.

A pyramidal tract lesion that produces hypertonia in the plantar muscles brings the latent deep reflex to the fore. As a result, brisk reflexive flexion of the toes occurs on every maneuver that brings about a sudden concussion and stretching of the plantar muscles. Here the same conditions prevail as on elicitation of the deep reflexes of the abdominal muscles. A sudden stretching of the plantar muscles may be brought about from many different points. The plantar surface of the toes, the muscles themselves, the heel, or even the pedal arch may be tapped. In the last mentioned method the plantar muscles sustain a sudden stretching due to the elasticity of the bony arch.

The goal of all these maneuvers is the same, namely, concussion and stretching of the plantar muscles. How this result is achieved is immaterial. Thus, all the different reflexes of the foot which are described as pyramidal tract signs and which consist of flexion of the toes are one and the same reflex. For instance, the reflexive phenomena described (Bechterew, 1901; Rossolimo, 1902; Mendel, 1904; Zhukowski, 1910; Guillain and Barré, 1916; Sicard and Cantaloube, 1916; Weingrow, 1933) represent the same reflex, the deep stretch reflex of the plantar muscles, elicited by different methods. This reflex is not in itself pathologic indicating a pyramidal tract lesion. It exists normally in latent form and occasionally under favorable conditions is seen distinctly in normal persons, as has been shown in many observations. By increasing the tonus of the plantar muscles, a pyramidal lesion merely makes the deep plantar reflex more apparent.

A very remarkable analogy exists between the reflexive reaction of the flexors of the toes and that of the flexors of the fingers. The latter also have a deep muscle reflex which normally is hardly discernible but which becomes apparent in functional hyperirritability and in a pyramidal lesion. Thus, a flexor reflex of the finger, that is reflexive contraction on sudden stretching of the flexors of the fingers, is in itself not a pyramidal sign. The numerous reflexes of the fingers that have been described (Hoffmann, about 1900; Bechterew, 1903; Goldscheider, 1903; Jacobsohn, 1908; Babinski, 1910; Troemner, 1912; Sicard and Cantaloube, 1916; Russetzki, 1925; Sterling, 1926; Kempner, 1926; and Rosner, 1935) and that have often been designated as pyramidal signs, represent one and the same reflex produced by different techniques. There is only one flexor reflex of the fingers, but there are many maneuvers to bring about the sudden stretching of the flexors followed by a reflexive bending of the fingers.

From this standpoint, neither the toe flexor reflex nor the finger flexor reflex can in itself be regarded as pathologic. Each represents a deep muscle reflex which exists in more or less latent form normally. General nervous hyperirritability or a lesion of the pyramidal tract merely makes the reflex more apparent—in the fingers more so than in the toes.

THE NEUROTIC CONFLICT BETWEEN THE INDIVIDUAL AND SOCIETY

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With its fondness for cults the world has in the past few decades reared temples to the gods of the normal. The cult of normalcy has gathered about itself priests and prophets who are loudly exhorting all who would be saved to worship at the shrine of perfection. Apostles swarm the land and invoke the spirits of science in their zeal to bring balm to those unfortunate souls who cannot fit into the procrustean bed of their own making. Mental hygiene and physical hygiene and spiritual hygiene and political hygiene and a host of other kinds of hygiene are fervently broadcast and foretell the coming of the millennium. The great gods have proclaimed it: all shall be of one measure, all shall be normal. All conflict shall cease, and the soul shall be at peace with itself and the world. *Mirabile dictu.*

To those who are less secure in their knowledge and less serene in their wisdom, the great fanfaronade has somehow failed to bring either balm or conviction. They wonder whether those who worship science loudest do not know least about it; whether the cult of the normal is not fast becoming the fetish of the stupid; whether the common yardstick was not fashioned of the smug complacency of the dullard; whether the gross compounding of the sheep and the goats will not become the measure and the refuge of mediocrity. While the great philosopher aims at perfection and the true scientist strives for accuracy and precision, both concede the limitations of wisdom and the fallacy of method. Both know the frailty of human nature, and each realizes that not only are perfect specimens rarely found in life, but that they are more likely to be preserved in museums. They both know that wonder and doubt are the beginning of wisdom, and marvel at the assurance of those who know so little. They wonder whether there is not danger in the worship of the elusive cult which is so vociferously heralded.

Lest the tenor of these remarks be misunderstood, let me state at once that I have no desire to defame the normal or to glorify the neurotic. I wish merely to point out, as others have done, the dangers of leveling downward by methods of questionable scientific worth. One might even venture the opinion that the elimination of those groups, who are deemed to be unfit because of their departure from what is commonly regarded as normal, may rob society of a great leaven which is necessary for its progress. And since much wealth and energy are being expended in heroic efforts to cure or to eliminate the neurotic and to make the world safe for mediocrity, it may not be unwise to pause for a moment and inquire what is meant by normal and what is understood by neurotic.

As is well known modern psychology has discarded hard and fast definitions.

* Address delivered at Pan-American Congress, 1937.

It has long ago given up the notion of faculties. We no longer speak of intelligence or memory as special faculties, but of types of intelligence and types of memory. In very large measure the same thing is true of the emotions. Even outspokenly emotional individuals are not equally emotional in all directions or under all circumstances. One person may calmly face danger to his own life and quail before a minor operation or in the face of danger to a beloved one. The same thing may hold true with regard to other mental traits. There is not a single mold or one perfect test, but a number of measures of human fitness. And if these are bemoaned as being less than divine, they are for that reason a good deal more human. Man as an individual being does not comply with the all or none law. He is not all good or all bad, all truthful or all lying, all respectable or all shabby, all kind or all cruel, all hypocrite or all intellectually honest, but a little bit of each. Much the more important question is how much of each. From this it follows that all people are not either perfectly normal or wholly abnormal; and one may agree with Freud that every normal is considerably neurotic and every neurotic very much normal.

A much better standard by which frail mortals can be measured is their capacity for adjustment to society. It is not altogether a question of how great a saint one can be in a desert, but how little of a sinner one can remain in a living, seething, complex civilization. Even without first hand knowledge one may venture the opinion that it probably is not very difficult to be perfect in a garden of Eden, provided, that is, there is no snake in the grass. The test of adjustment brings the problem down to earth, and reduces the question to one of individual versus social adaptation.

If the social-biologic view of the causation of the neuroses is correct, it may be conceded that they are born of the conflict between the individual and the group. In the scheme of nature one constantly observes a struggle going on between the two. Biologically viewed the preservation of the group is the ultimate goal and much the more important in the scheme of evolution. As has been repeatedly pointed out, the intensity of one's individualism may be measured by his or her propensity or ability to rebel against social forces, while the index of one's gregariousness may be gauged by the extent of one's ability to mold the individuality to the demands of the social group. He who cannot openly revolt against those demands or placidly accede to them begets an inner conflict which manifests itself in departures from what is commonly regarded as normal. The needs for adjustment become greater and greater as civilization progresses. It is commonly agreed that in primitive society, which is fairly inelastic in its social organization, there is less opportunity to rebel against powerful social taboo. The observation has also been made that there is comparative absence of what we regard as neuroses. From all that we know there is reason to believe that neuroses increase with the progress of civilization. If this be true one may affirm that modern neuroses are a product of civilization and a "luxury" which only civilized man can afford. To put it differently, the neurosis is the tribute which society pays to the individual for levying on his ego to form a complex social order.

The struggle between the individual and closed social systems which has been going on from time immemorial, is raging with peculiar force just now. But the question is not who will be the victor and what will survive, but what will serve best both the individual and society. The two aspects of the conflict are sharply brought into view at the moment in countries where dictatorships and regimentation would snuff out the individual altogether and in liberal democracies which still foster the unhealthy philosophy of each man for himself and the devil take the hindmost. The real problem is, how much individual freedom and development can be fostered in a well organized society and at the same time insure a healthy, just, free and ethical social order and how far selfish individualism must be curbed without crushing that individuality which is so necessary to social growth. If society is so regimented, stratified and congealed so as to permit of no fermentation or doubt or criticism or even revolt, the individual is sure to be fashioned into a docile robot by a dull bureaucracy; just as unbridled individualism is sure to bring anarchy and chaos. But it should be added that this concept is not new, that the conflict is as old as life, that it is the crux of education and ethics which begin with the cradle, and that it continues as long as man lives and society endures. As soon as the child begins to understand he is taught to curb his selfish and anarchistic impulses and to learn how to be a social human being. In some respects education consists of a series of don'ts from the cradle to the grave, of injunctions to inhibit antisocial acts; but one must ever guard against regimentation, against stunting of individuality, against snuffing out freedom, and against destruction of the will and of the creative spirit. Totalitarianism can well be an infinitely more malignant social neurosis than any yet born out of one isolated personality. The neurotic individual is much less dangerous than a neurotic society.

Much of what has been said applies, of course, to conscious conflict and leaves out of the reckoning modern psychopathology which justly lays so much stress on unconscious conflict based on primitive instincts. But it is not always a question of deep-seated conflict. Not everybody is cast in great molds, and heroic conflict is not the lot of most people. The lesser vicissitudes of daily life, which beset everybody in complex civilizations, expose every one to terrific pressure which, when it affects certain types of persons, expresses itself in a neurosis. The constant necessity for submission to authority; the exigencies of the social and economic order; the general struggle for existence; the great need for adjustment to love life under moral and ethical standards which interfere with, if they do not thwart, primitive instinctive desires for gratification; the difficulties inherent in the marital state which aims to harmonize but fails to gratify conflicting social needs and personal longings; the emotional fermentation involved in clinging to or departing from religious restraint and ritual; all constitute a battlefield which lasts as long as life and claims unnumbered casualties among those who cannot successfully engage in the combat. The relationship between parents and children is so replete with possibilities of conflict that it frequently fertilizes neurotic soil and brings forth crops of neuroses. For children are not only the beneficiaries but also the victims of their parents.

In all individuals there is this great need of hurdling difficulties, all the way from the cradle to the grave, which stand in the way of adaptation to reality. Most people do so effectively, even if some get hurt in the process. Inability to make the hurdle often leads to flight from reality into the arms of fantasy and neurosis. There is regression, so to speak, to infantile ways, to easier modes of adaptation. Given sufficient stress of circumstance all of us are capable of becoming neurotic. Ordinarily most people can stand considerable buffeting without showing signs of cracking up.

It has been frequently pointed out that the punctilious scholar, the meticulous investigator, the rigorous logician, each betrays in a useful way the compulsive character traits of the neurotic. The poet who can withdraw into his ivory tower, the philosopher who can abstract himself for his lucubrations, the inventor who shuts himself off from society, each shows an introvert or shut-in character type which is known as schizoid or split personality. An exaggerated form of such a mental reaction may result in an aberration which constitutes insanity. On the other hand, the voluble babbit, the band-wagon joiner, the ubiquitous good fellow, the enthusiastic back-slapper is generally an extrovert and sometimes a bit manic. But many a person who creates and successfully undertakes apparently insuperable tasks is goaded on by a hypomanic impulse which if exaggerated and not purposively directed may constitute mania. Even "perversions" of a mild character may underlie normal conduct. Thus, while exhibitionism is justly looked upon as a perversion, in its more social aspects it shows itself in the ostentatious display of male prowess, in feminine coquetry, and in the mannerisms of some actors, writers and orators. Not only is the pugnacious instinct of the male a form of sadism, but this trait in a moderate degree characterizes masculine love making. The very act of being in love often implies a submissiveness, a joy in suffering which is but a mild expression of actual masochism. Nor is it such a far jump from the romantic adoration of the kerchief of one's beloved to the pronounced state of fetishism.

It is not the object of this essay to paint the neurotics in glowing colors or to minimize the grave problem which this group presents to society. Not every neurotic is a good and great man or a useful person, and one need seek no comfort in a neurosis. Decidedly it is not good to be neurotic or to be glad that one is. Most neurotics are unhappy themselves and make others unhappy. They neither understand their own illness, indeed do not realize that they are sick, nor are they understood by most people. They generally misdirect or retard the social wheel, although they sometimes accelerate it. In some respects the neuroses constitute a graver problem to society than the psychoses, for the psychotic generally breaks with his environment and automatically eliminates himself, whereas the neurotic retains his contact with the group and frequently disrupts it. The neurotic always taxes the ingenuity of the physician, and it is no exaggeration to say that in no branch of medicine are so much tact, art, skill, knowledge, assurance and understanding needed as in the management of the neuroses.

But it is necessary to insist that a neurotic character trait or even a mild

neurosis does not quite constitute an abnormal personality. Some degree of neurosis may actually add to one's mental stature and may perhaps be regarded as the salt of personality. A certain amount of inner conflict is the necessary mainspring of useful activity. Even a pronounced neurosis is not incompatible with great usefulness to society. Great humorists, brilliant scientists and inventors, religious leaders, social rebels, the vast majority of creative artists and an untold number of others who have contributed to spiritual and material progress, have been neurotic or actually suffered from outspoken neuroses. Unless one has a certain amount of inner and outer conflict which he can sublimate into socially useful activities, he is not likely to rise above the level of a cog in the social wheel. To create one must ferment within if not actually suffer, for conflict is a source of creation. Finally, to have a neurosis at all one must have a sufficiently developed conscious and unconscious mind between which conflict may go on and out of which character and personality can be developed. Dray horses do not develop neuroses, at least not interesting ones; spirited race horses sometimes do. Even mules can become stubborn and kick.

The frustrations of love life which punctuate adult existence, which thwart the socially useful institution of marriage, are conceded by most observers to be potent factors in the causation of neuroses. The general incompatibility of marriage, which serves the needs of the family, with the erotic and erratic impulse of the individual, which brooks no restraint, tests the mettle of spirited individuals and often shatters morale and with it social bonds. For powerful impulses cannot be easily bridled; and it is generally conceded that given a vigorous, creative mind one may infer a powerful sex drive. It is probably equally true that he who has a good sense of humor not only shows deep intelligence but an equally deep and stirring sex impulse. A humorless man is generally without love impulses or other deep feelings. It is doubtful whether a really great man can be a good husband or even a perfect lover—except for a brief moment. But it is equally true that perfect husbands are mostly dull men, and model sons make wretched lovers and worse husbands.

It would be easy to call to mind names of great men who have been neurotic and have contributed so much to the progress of mankind. In fact it would be more difficult to match that array with an equally imposing group who would today be regarded as normal. One need not offend sensibilities by mentioning prophets who have created great religions. Some of them would not only be regarded as neurotic but hounded as mad. The name of many a sinner, who underwent sudden conversion and shifted from profligacy to sainthood, illumines the pages of religious history and is the glory of sects.

What if Benvenuto Cellini was a rake and Francois Villon a vagabond? Or that Dostoyefsky had fits and that Leonardo da Vinci knew not woman yet painted a most glorious effigy. Does it matter now that Poe drank or how Whitman lived? How much did Lincoln's brooding moods and his unhappy love life contribute to his greatness? For every poet who was "normal" at least ten were maladjusted. They may have been mad, but theirs was a sublime madness. Philosophers may have been queer and unsociable but they have con-

tributed to human thought. Perhaps one of the reasons why philosophers and metaphysicians are scarce nowadays is that scholars have become so desperately normal.

But it is not only among individuals that conflict and fermentation and suffering bring forth nervous reactions. Whole peoples sometimes undergo similar changes. Many have done so and left deep marks on the course of time. Some have been noble adventures. The French Revolution was indeed a bloody orgy, a wild emotional frenzy, destructive in its blind fury; but out of unendurable suffering came a purging of the spirit, a shattering of the crust of ages, a freeing of the enchained soul. Thomas Paine and even the respectable Samuel Adams fired with sparks from their own souls the conflagration which was the American Revolution. No matter that other social and economic motives spurred the rebels on, an inner flame which could not be quenched by cries for normalcy was there all the time.

But it is worth noting that the revolutionary often is a brooding, frustrated, discontented soul, a socially maladjusted individual. If he happens to be at the same time a true spirit with a fundamentally healthy mind and is goaded on by sound social impulses he may succeed in freeing himself and others from shackles which hamper progress. But if he carries over into his social activities the gnarled threads which warped his emotions he may only succeed in imposing on society the neurosis which is his own.

Even a cursory reading of history will convince one that many social upheavals were group neuroses, if not sheer madness, and bequeathed only suffering. Indeed there were whole ages which may now be regarded as mad. Witness the religious, political and other social persecutions, and the days of witchcraft. In many ways the social neuroses were but a reversion to primitive ways of life, a regression to emotionally infantile behavior, cruel in practice and malignant in effect. They were motivated by fear and hate and vengeance; they fostered cringing and suspicion and nurtured the lowest and most destructive of human instincts. Lying and hypocrisy and cruelty perforce were made the daily practice, indeed elevated into moral principles, independent thinking was banned as a subversive activity, and the individual was crushed and left prostrate. The evil lay in the fact that whole philosophies of life, which were as false as they were immoral, were reared and imposed on spiritually defeated men, and genuine thinking was made a crime. Life became tyrannical, the social order often fell a prey to cunning, clever and unscrupulous men who knew how to exercise their base cruelty in the guise of great leaders. The state as an ideal fiction was set up, and merely served as a convenient subterfuge to snuff out the individual.

It requires no great or deep thinking to recognize in the modern dictatorships a revival of the ways of the older tyrannies. Now, too, the state is made the supreme fetish which the individual is to worship without questioning. The false philosophy that the state is something which exists of and by itself is made supreme. As if there ever can be a state without individuals, as if a state can ever be better than the men and women who go to make it up. What if the evil leaders are themselves abnormal, cunning and cruel and serve their own ends in

the guise of public servants? It must not be questioned even for a moment. The first article of the new decalogue is, thou shalt not think. And there is no thinking; only fear and hate. The social neurosis alone is to be supreme.

The analysis of the evils of totalitarianism need not blind one to the numerous evils and injustices existing in the liberal and democratic way of life. But with all its frailties it is a human and a decent way, and there is a fundamental difference. The philosophy of all democratic government is based on the worth of the individual. The ideal of the state presupposes a just and ethical system in the interest of the individual and promises him free development at the same time that it demands his contribution to the welfare of society. It does not seek by sheer force to impose itself on others or to jam down the throats of unwilling people ideas which they cannot swallow. It does not constantly invoke the immoral principle that the end justifies the means. It does not glorify cruelty, lying and hypocrisy and set them up as the way of life. There is no fatal impulsion in democracies to construct philosophies out of stupidities or to fashion principles out of falsehoods. In short, while individual neuroses do exist, they are not made the basis of life and are not transmuted into one all inclusive social neurosis.

But there really is no cause for despair. Serious as the struggle is and grave as the threat appears to be, the individual is nonetheless sure to survive. And not merely because evil cannot prevail, for it can, and has again and again prevailed over long periods of time, but because the human animal is tough and he ultimately does learn. Progress is slow and suffering is the price of its achievement, but out of conflict and suffering personality is fashioned. Out of the same conflict also come individual neuroses, but, provided society does not become neurotic, there is no danger that man will cease to progress and remain dull normal.

In the beginning there was fear and ignorance, and then came faith and morals and a certain way of life. Later arose curiosity and wonder and doubt, and out of them grew knowledge and wisdom and understanding and an ethical way of life. On the highway to progress through which man struggled upward there were many hills and valleys and rough and winding roads and blind alleys. At many points on this highway some stumbled and fell and others passed on. And neurosis was the price which both the individual and society had to pay at various turns. For neurosis is the tribute which the group sometimes pays to the individual for levying on his ego to make him social.

EXPERIMENTAL TUMOR OF THE HYPOPHYSIS OF THE WHITE RAT[1]

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In a previous publication (1) concerned with the production of experimental tumors of the central nervous system in the white rat brief mention was made of the observation of adenomata of the hypophysis in rats which had been injected with styryl 430, a mildly carcinogenic substance. Previously Oberling, Guérin and Guérin (2) had described pituitary adenomata in white rats into whose cerebral cortex crystals of dibenzanthracene had been implanted. More recently attempts have been made to produce such adenomata by the injection of estrogenic hormones. Weil and Zondek (3), however, have pointed out that such "adenomata" produced by the injection of estrogens do not represent true benign tumors. They are cellular hyperplasias of the original pituitary cells without neoplastic transformation. The large size of the pituitary seen following injections of excessive doses of the hormones is partly due to intraglandular hemorrhages.

Implantations of carcinogenic substances into organs other than the brain occasionally lead to the formation of small pituitary tumors. Perry and Lockhead (4) reported three examples in female mice, into the mammæ of which dibenzanthracene had been implanted. Spontaneous occurrence of pituitary tumors in rats appears to be extremely rare. In our own stock we have never observed such pathologic changes during the last six years during which brain autopsies on at least five hundred rats were performed. Fischer (5), however, saw three hypophysial tumors in 200 to 300 autopsies, two of them in two female rats, three years old, and one in a male rat. Two of the tumors were composed of atypical cells. In mice Slye (6) and Gardner (7) each observed one primary tumor of the hypophysis. The former authors saw only two primary neoplasms in the brains of 11,188 mice: a papillary ependymal adenoma and an "endothelioma." The tumor described in the hypophysis of a fourteen month old mouse formed a "barely visible mass of reddish tissue which microscopically consisted of about equal parts of dilated, thin walled vessels and a cellular growth . . . the cells of which had large vesicular nuclei, round or oval, with little cytoplasm, and no mitotic figures were found."

Wolfe (8) studied the presence of pituitary adenomata in old rats. In 52 young male rats, 60 to 300 days old, no adenomata were found. In 1 out of 17 old male rats, 540 to 900 days old, an "hemorrhagic adenoma" was found in another "adenomatous foci." In 38 female rats of the "Vanderbilt strain" (497 to 729 days old) eleven "adenomatous pituitaries" were found; in 38 old female rats of the "Wistar strain" this number amounted to 26 (68 per cent).

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The accompanying table gives a review of the clinical data of three rats in our series into whose brain carcinogenic substances had been introduced.

DESCRIPTION OF ADENOMATA

Rat 1. Into the brain of this first rat, a six month old female, the emulsion of a rat brain was injected. The emulsified brain itself had been injected 235 days previously with styryl 430, a mildly carcinogenic substance. Rat 1 survived for 322 days. At autopsy the darkly reddish hypophysis was seen protruding over the sella turcica. It measured approximately 2 mm. in the antero-posterior diameter and 3 mm. in the lateral diameter (fig. 1 A). (These measurements and the following ones are from sections of paraffin embedded material.) No brain tumors were found, and there was only a mild glia proliferation surrounding the walls of the lateral ventricles. The enlarged anterior lobe of the pituitary surrounded the infundibulum and the infundibular process, both of which showed no pathologic changes. The pars intermedia, too, appeared normal. The individual cells of the enlarged anterior lobe measured about 7 micra and their round nuclei about 4 micra. Most of them contained a pale

TABLE I

RAT NO.	INJECTED	AGE	SEX	DURATION	WEIGHT	
					Original	Final
		days		*days*		
1	Transplant from rat injected with styryl 430	492	F	322	182	242
2	Styryl 430	473	M	293	314	357
3	Methylcholanthrene	450	M	359	170	310

staining area suggesting a negative Golgi apparatus (fig. 1 B). The nuclei were rich in chromatin; no mitotic figures were seen.

Rat 2. Into the brain of a six month old male rat 0.1 cc. of a 1 per cent solution of styryl 430 was injected. This rat did not show any appreciable increase in weight, in comparison with other rats injected in a similar way. After about two and a half months a mild exophthalmus appeared which remained rather stationary. At autopsy a large, bulging hypophysis was found which was easily removed from the enlarged sella turcica. It measured approximately 5 mm. in the lateral diameter, 3 mm. in the dorso-ventral diameter and 3 mm. in the antero-posterior diameter. The enlarged anterior lobe compressed the infundibulum (fig. 2 B). In the meninges surrounding the infundibulum and the floor of the third ventricle (fig. 3 C) dye particles were found, enclosed in large scavenger cells and surrounded by a loose fibrillary meshwork. There was mild glia proliferation in the tissue surrounding the third ventricle (fig. 3 D). The anterior lobe tumor itself consisted of two different masses: a central core measuring approximately 3 mm. in diameter and two lateral lobes. The latter contained normal anterior lobe cells with well stained eosinophilic cells, though the cells seemed to be compressed by the extending central mass (fig. 3 B). The latter was composed mainly of large polygonal cells which stained faintly blue

in Haterius stained sections. They measured approximately 20 micra in diameter. Their nuclei were 7 micra in diameter; they were vesicular and contained a sharply defined nucleolus (fig. 3 A). There was no definite connective tissue meshwork characteristic of the normal anterior lobe. The transition from the central mass to the peripheral zone was gradual and there was no membrane separating the two (fig. 2 B).

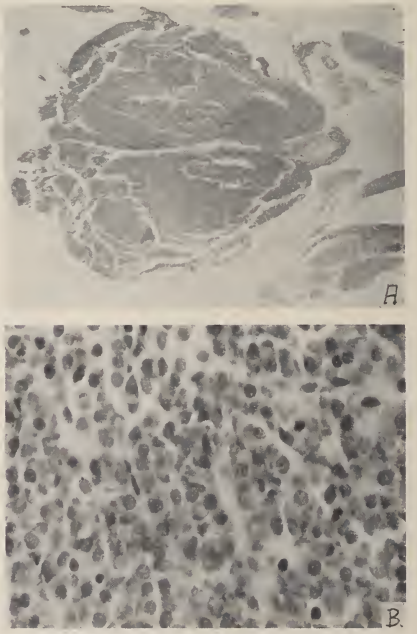

FIG. 1. Rat 1. A. Horizontal section of enlarged hypophysis. Cresyl violet-eosin stain. Magnification 25×. B. Anterior lobe cells. Same stain as A; magnification 780×. For detailed description of these photomicrographs and the following ones, compare text.

Rat 3. Crystals of methylcholanthrene were deposited into the infundibulum of a three months old male rat with the help of the Horsley-Clarke stereotaxic instrument. During the sixth and seventh months following this operation the weight of this rat remained stationary between 290 and 294 grams. It then gradually increased to 310 grams. During the twelfth month following the operation it was apparently sick, taking little food and losing weight. At autopsy a large reddish mass was found at the base of the brain. It was adherent to the base of the skull and extended from the anterior border of the pons beyond

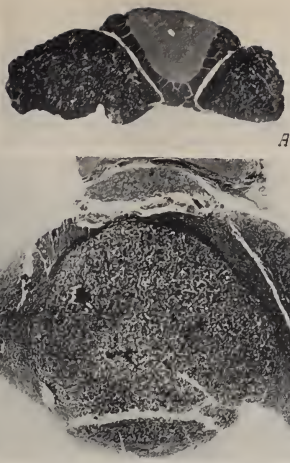

Fig. 2. Rat 2. A. Normal hypophysis, horizontal section. Haterius stain; magnification 30×. B. Adenoma of anterior lobe in rat 2. Staining and magnification as in A.

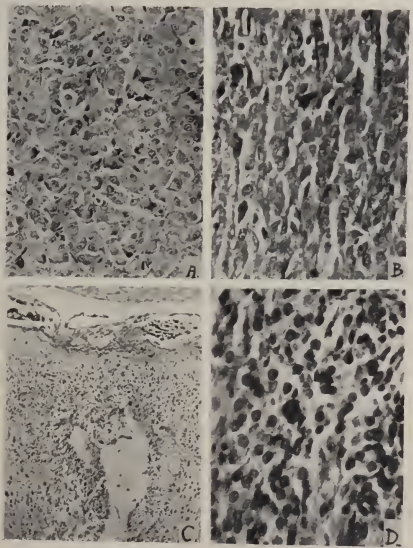

Fig. 3. Rat 2. A. Cells from the center of the adenoma. Haterius stain; magnification 350×. B. Cells from the periphery; Haterius stain; magnification 690×. C. Section through the upper part of the infundibular process; Haterius stain; magnification 105×. D. Glioma nodule in wall of lateral ventricle. Van Gieson stain; magnification 720×.

the chiasm. Laterally it was bordered by the inner surfaces of the temporal lobes (fig. 4 A). In sagittal sections (fig. 4 B) this tumor mass was composed of an unhomogeneous central mass (fig. 4 B, 2 and 4) and a larger anterior and posterior third. Judging from the anatomic landmarks and the histologic appearance it was evident that the anterior and posterior thirds were derived from the anterior lobe of the pituitary, while the central part comprised the

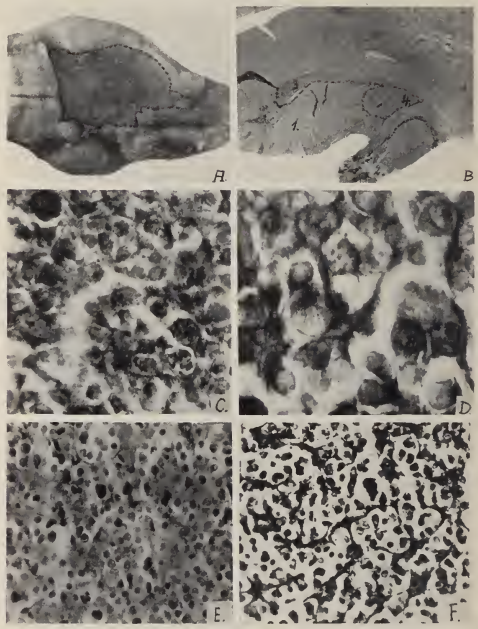

FIG. 4. Rat 3. A. Photograph of the base of the brain. B. Sagittal section through tumor and base of brain. Kanzler's modification of the Hortega stain for microglia; magnification 19×. C. and D. Cells from the anterior lobe tumor. C. Haterius stain; magnification 760×. D. Azan stain; magnification 1250×. E. Cells from the periphery of the anterior lobe tumor; cresyl violet-eosin stain; magnification 560×. F. Same as E; Holzer stain; magnification 430×.

pars nervosa (fig. 5 A, 3) together with the pars intermedia and pars tuberalis (fig. 5 A, 2). The median eminence was transformed into a loose tissue continuous with the main tumor mass (fig. 5 A, 1). These different areas presented the following histologic pictures:

A. The anterior and posterior thirds were composed of islands of cells separated by strands of connective tissue, closely imitating the arrangement of the

normal anterior lobe (fig. 4 E, F). In the center of the tumor mass the large cells measured approximately 17 micra in diameter; only a small rim of cytoplasm surrounded the large nucleus. The cytoplasm stained a homogeneous blue in sections stained with the Azan and Haterius methods, but no eosinophilic cells could be found (fig. 4, C, D). In the most lateral sections from the periph-

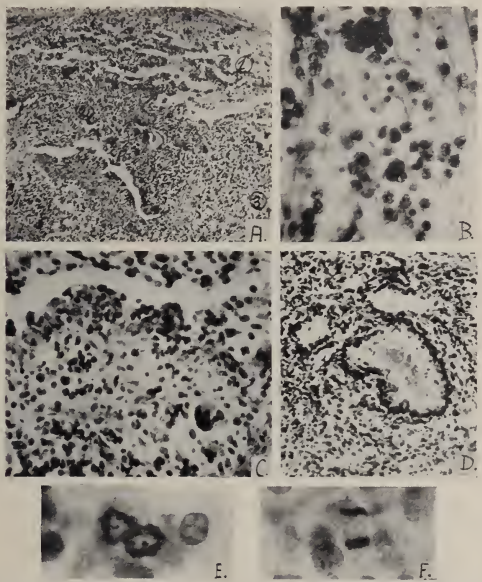

FIG. 5. Rat 3. A. Sagittal section through median eminence with adjacent tumor. 1) median eminence; 2) corresponding to pars tuberalis in normal brain; 3) corresponding to infundibular stalk. Van Gieson stain; magnification 72×. B. Cells from the median eminence. Van Gieson stain; magnification 560×. C. Papillomatous protrusion in part of tumor corresponding to normal pars tuberalis. Van Gieson stain; magnification 580×. D. Cyst formation; Van Gieson stain; magnification 205×. E. Mitotic figures from outer zone of anterior lobe tumor. Cresyl violet stain; magnification 1700×. Mitosis in metaphase. F. Mitotic figure from infundibular stalk; cresyl violet stain; magnification 1610×. Mitosis in telophase.

ery of this tumor numerous mitotic figures were seen (fig. 4 E), most of them in the metaphase (fig. 5 E) and fewer in the telophase (fig. 5 F).

B. The portion of the tumor which corresponded normally to the infundibular stalk and process (figs. 4 B, 2 and 5 A, 3) differed from the preceding picture. It consisted of loosely arranged smaller cells with nuclei measuring from 8 to 10 micra (fig. 6 A and B). The scanty cytoplasm was not sharply defined but extended in many fibrillary processes. These could be well demonstrated in

preparations stained with the Haterius method and the Kanzler modification of Hortega's microglia stain (fig. 6 C). The peripheral extension, probably corresponding to the infundibular process was more vascular than the central end (fig. 4 B, 2). This part of the tumor, therefore, should be classified as a glioma of the neurohypophysis.

C. The region of the tumor corresponding normally to the pars tuberalis (figs. 5 A, 2 and 4 B, 4) formed peculiar papillary protrusions, covered by several layers of small epithelial cells (fig. 5 C). The center consisted of small, epithelioid cells of manifold sizes, intermingled with a few giant multinuclear cells. There were several cyst-like structures, lined by two to three rows of small cells with dark staining nuclei (fig. 5 D).

D. The region ordinarily occupied by the pars intermedia could be recognized by its different staining reaction. It did not, however, contain any of the original typical cells, but presented a wall of connective tissue fibers intermingled with blood vessels and nuclei of different shapes and sizes.

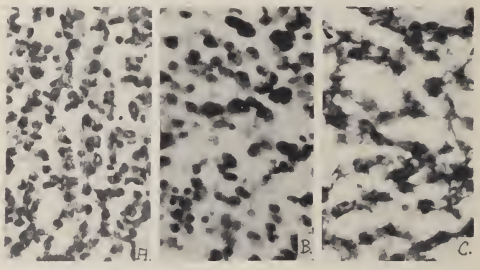

Fig. 6. Rat 3. Cells from the part of the tumor corresponding to the normal pars nervosa hypophysis. A. Hematoxylin-eosin stain; magnification 500×. B. Van Gieson stain; magnification 620×. C. Haterius stain; magnification 750×.

E. The median eminence, too, had lost its normal appearance. It consisted of a loose cellular tissue (fig. 5 A, 1). The cells (fig. 5 B) resembled those found in the infundibulum (fig. 6 B). They contained a small rim of cytoplasm surrounding round nuclei of different sizes, measuring from 5 to 15 micra, and large multinuclear giant cells. The tumor invaded the anterior hypothalamus for a short distance. The posterior hypothalamus, the optic chiasm and the optic tract, however, were not invaded. These tissues barely showed a reaction to the neoplastic disease of the environment. The pia-archnoid, separating the tumor from the base of the brain was somewhat thickened, but there was no glial response in the underlying brain tissue.

COMMENT

In view of the findings of spontaneous pituitary adenomata in old rats, there could be doubt whether the first two cases should be classified as "experimental tumors" following the injection of carcinogenic substances, though their age

(492 and 472 days respectively) was somewhat below Wolfe's minimum age of 540 days. On the other hand, spontaneous, grossly visible pituitary adenomata had not been observed previously in our strain. Rat 1 might also be ruled out as experimental tumor for the reason that it had been injected with the transplant from a brain which eight months before had been injected with a carcinogenic substance and which grossly had not shown tumor formation. In rat 2, however, the dye particles of styryl 430 were found surrounding the base of the brain and the enlarged hypophysis. Besides the dye had induced small gliomata in other parts of the same brain (fig. 3 D).

No doubt should remain that the neoplastic disease in rat 3 was actually induced by the methylcholanthrene which had been placed previously in this very region with the help of the Horsley-Clarke stereotaxic instrument. It is the first case of its kind reported and it again lends support to the working hypothesis which one of us made the basis of a previous publication (1): "The potency for malignancy is a universal cell characteristic."

SUMMARY

Three cases of pituitary adenomata are reported in white rats in which carcinogenic substances had been implanted into the brain. In one rat these adenomata of the anterior lobe were combined with gliomata of the brain, and in a second rat with tumor of the pars nervosa and of the pars tuberalis.

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NEUROLOGICAL MANIFESTATIONS OF CARCINOMA OF THE LUNG

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Anyone who has had the opportunity to observe the increasing number of cases of cancer of the lung must be struck by the prominent role which neurologic symptoms play in their clinical course. As long ago as 1870 Eberth (1) described and clinically verified post-mortem meningeal metastases in a case of pulmonary carcinoma; since then there have been numerous recordings of metastases in every portion of the nervous system, which have simulated a great variety of neurologic conditions. So prominent may these symptoms be that a considerable number of patients are less affected by their pulmonary tumor than by the painful and disabling involvement of nerve tissues or organs. In some cases, in fact, the tumor in the lung may be actually dormant and so devoid of symptoms that evidence of its existence may only be found in a disturbed function of the brain, the spinal cord, the meninges or the peripheral nerves.

Some idea of the variety of these disturbances whose clinical implications we propose to discuss may be gathered from an enumeration of the neurological disturbances which we have personally observed, as follows: 1) Horner's syndrome, 2) syndrome of brachial plexus involvement, 3) recurrent nerve paralysis, 4) phrenic nerve paralysis, 5) intercostal neuritis, 6) radiculitis, 7) polyneuritis, 8) transverse myelitis, 9) brain tumor (cerebral and cerebellar), 10) subarachnoid hemorrhage, 11) pseudo-tabetic syndrome, 12) meningeal carcinosis, 13) psychic disturbances.

In addition we may add the following syndromes which are recorded in the literature: 1) syndrome of tabo-paralysis, 2) ophthalmoplegia, 3) hemiplegia, 4) syndromes of cranial nerve paralysis due to basal meningeal involvement, 5) Landry's paralysis, 6) sciatic syndrome.

This study is based upon 300 cases of carcinoma of the lung whose diagnosis was confirmed either during life or at autopsy. In 62 of these cases there were clinical evidences of involvement of the nervous system, roughly over 20 per cent. Large as this percentage is, its importance in the whole clinical picture is enhanced by the fact that in a fair number the nerve changes were of a serious nature and often contributed to the early death of the patient. Furthermore, pain and a variety of other nervous symptoms imparted to the disease much of its dreaded character.

The neurological complications of carcinoma of the lung are determined by the manner in which these tumors spread from their point of origin. From this point of view one may recognize two distinct types of tumors which may for convenience be designated as a circumscribed or peripheral form and an infiltrating or bronchial form (2).

The former begins usually near the periphery of the lung whence it extends

by concentric growth to its pleural surface until it invades the adjacent soft tissues and bones of the chest wall. This tumor produces a minimum of pulmonary symptoms and as it does not originate in a major bronchus it is not discovered by bronchoscopic examination. It rarely invades the regional lymph nodes but when it does so this occurs only late in the course of the disease. It metastasizes mainly by way of the systemic circulation. The infiltrating tumors usually begin in a major bronchus or occasionally in a branch bronchus. Because of this origin symptoms of bronchial irritation such as cough and expectoration occur early in the disease and are apt to continue throughout it. This tumor metastasizes very early into the bronchial lymph nodes and later by way of the circulation shows a great tendency to deposit cancer cells in the skeleton and in the nervous system. Unlike circumscribed tumors it does not have any extra-pulmonary invasive characteristics and its growth is confined to the lung and pleura. Circumscribed tumors are much less numerous than the infiltrating variety, the proportion being roughly one of the former to three of the latter.

ANALYSIS OF NEUROLOGICAL SIGNS AND SYMPTOMS

We present herewith in detail the individual neurological phenomena which we observed in three hundred cases of carcinoma of the lung.

Recurrent nerve paralysis

This was the commonest neurological sign associated with carcinoma of the lung. It occurred in twenty-one cases of infiltrating tumors and only once in the circumscribed variety. The left recurrent nerve was affected in all but two cases for well understood anatomical reasons. Apparently vocal cord paralysis is always due to pressure of metastatic deposits in the intrathoracic lymph nodes and it is therefore an indication that the tumor is inoperable. It also permits the inference that one is dealing with an infiltrating new growth of bronchial origin. Hoarseness was in most cases the only symptom of this complication, except in two cases in which it was absent. In these cases paralysis of the vocal cord was only discovered during a routine examination of the larynx. Such a compensation for the paralysis of one vocal cord is well known to laryngologists. It is apparent therefore that the absence of symptoms of cord paralysis in a case of pulmonary new growth cannot be taken to exclude metastases in the bronchial lymph nodes.

The unusual occurrence of a right recurrent paralysis in two cases was readily explained by the autopsy findings. Owing to the higher origin of the nerve on the right side it is not ordinarily involved by cancerous nodes at the hilum as is the case with the left nerve. However, in exceptional cases the right paratracheal group of lymph nodes is very much enlarged together with their extension upward toward the larynx. When this occurs the right recurrent nerve may be compressed. In these two cases autopsy showed a massive enlargement of the paratracheal nodes which had been previously visible on the Roentgen film. In one instance the nerve was invaded at its very entrance into the larynx by a cancerous node. The one case of recurrent paralysis associated with a cir-

cumscribed tumor is exceptional enough to warrant comment. The occurrence of glandular metastases in this type of tumor, at least in its early stage, is so rare that it may be questioned whether the recurrent paralysis was not here due to a direct invasion of the nerve by the growth.

Horner's syndrome

This syndrome was found eleven times with circumscribed tumors but only four times with the infiltrating variety. It was frequently an early symptom of the growth. In contrast to lesions of the recurrent nerve this syndrome is predominantly due to direct invasion of the nerve tissues by a tumor of the circumscribed type. In these cases the tumor was always situated in an upper lobe usually in its paravertebral portion where it lay in proximity to both the brachial plexus and the sympathetic. In the case of the infiltrating tumors on the other hand such a direct involvement never occurs. Of the four instances of infiltrating tumors in which Horner's syndrome occurred the primary tumor was situated in the lower lobe in two cases. Here there can obviously be no question of direct invasion of the cervical sympathetic ganglia by the growth. Horner's syndrome, as is the case with other neurological manifestions of infiltrating lung tumors must therefore be ascribed to the pressure of metastatic foci, distant from the primary tumor. In proof of this it was possible in some of the cases to feel hard lymph nodes just above the clavicle. In the case of circumscribed tumors the sympathetic nerve was naturally always involved on the same side as the tumor; on the other hand with infiltrating growths this was not necessarily so.

The symptoms which resulted from an invasion of the cervical sympathetic were with two exceptions of a destructive nature and resulted in enophthalmus and a contracted pupil. In one case there were symptoms indicative of an irritation of the ganglion, namely, dilatation of a pupil with hyperhidrosis. In several cases there was a noticeable anhidrosis of the face and neck. It is worth recording that in one case with a destructive lesion of the ganglion there was marked stimulation of the sweat glands on that side.

Involvement of the brachial plexus

One of the commonest neurological complications which we observed is an invasion of the brachial plexus by the tumor. Herein we see once more a manifestation of the different paths these tumors take in involving the nervous system. It is a result of the direct growth of the tumor through the pleura near the upper aperture of the chest whereby the adjacent strands of the brachial plexus are immediately invaded. It is thus characteristic of the circumscribed tumors in which it occurred nine times. Contrariwise, it was never observed with the bronchogenic infiltrating growths. Confirmation of this pathway of invasion was found in the fact that invariably plexus symptoms were associated with tumors in the apex of the lung, usually in its paravertebral portion. In six of the cases one or more ribs were locally eroded by the tumor and in two instances there was additional destruction of the adjacent vertebrae. These changes could be readily seen on the Roentgen film.

The symptoms of plexus involvement showed great uniformity consisting usually of pain down the entire extent of the arm to the fingers accompanied at times with muscular weakness. In some instances there was in addition pain in the shoulder and in the upper part of the chest. In three cases the nervous symptoms antedated any clinical indication of pulmonary disease and in one case the pulmonary tumor remained latent. It therefore happened that the initial diagnosis in a number of cases was arthritis or radiculitis until the tumor made itself locally manifest in the lungs or was discovered by Roentgen examination.

Phrenic nerve involvement

The phrenic nerve was affected in twelve cases of cancer of the lungs. With the exception of one case, in which there was intractable hiccough, this complication did not induce any symptoms and it was discovered only on Roentgen examination. It occurred eight times with infiltrative tumors and in all but two cases they were in the upper lobe. In most cases it was presumably due to a metastatic involvement of the regional lymph nodes.

Involvement of peripheral nerves

A considerable number of patients complained of a variety of pains which, it could be ascertained, were due to pressure of the tumor on its metastases to peripheral nerves. The location of the pain was determined by the method of growth or metastasis of the tumor. In the circumscribed variety, pain in the chest, located usually at the site of the growth was often due to the direct extension of the tumor into the pleura, ribs and intercostal nerves. In view of the common situation of this tumor on the posterior aspect of the lungs, the pain was commonly experienced on the back of the chest. In contrast with that of simple pleural involvement, the pain due to erosion of the ribs and intercostal nerves was continuous, agonizing and not easily relieved by drugs. It occurred in seven cases and was sometimes associated with the pains of brachial plexus disease. At times local erosion of ribs afforded visual Roentgen evidence of this complication. Pain of this variety was much less common with infiltrating tumors. Here it was caused by metastases to various dorsal and lumbar vertebrae with resulting pressure on nerve roots. The clinical picture of radiculitis was thus reproduced in addition to local pain and tenderness from bone destruction. This occurred in only three cases.

INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

The cerebrospinal manifestations of carcinoma of the lung offer an interesting clinical study. Because of their bizarre features they have long aroused the interest of neurologists and have occupied a prominent place in the literature of malignant tumors of the lung. In the earliest recorded cases it was already commented upon that the symptoms of involvement of the central nervous system were apt to appear at a time when few or no clinical indications of the primary tumor of the lung were present. We can amply confirm this observation in the present series of cases. Fourteen patients had outspoken symptoms of central nervous system disease, the metastatic origin of which was proven either

by autopsy or operation or could reasonably be inferred from the neurological changes observed. Nine of these either had no symptoms of a pulmonary growth or the symptoms were of so insignificant a character as to be completely overshadowed by the neurological complaints. For this reason in several instances, craniotomy was performed in the mistaken belief that there was a primary brain tumor, an error which was either discovered at autopsy or by a later Roentgen examination of the lungs.

Lesions of the spinal cord

There was one case of compression myelitis at the level of the sixth dorsal vertebra with a rapidly developing flaccid paralysis of the lower extremities and corresponding sensory symptoms with a complete cerebrospinal block at that level. This was due to a metastatic deposit in the vertebra involving also the dura. We note here that this patient had no pulmonary symptoms although he had a large infiltrating tumor arising from the right main bronchus. Although there were a number of other cases which exhibited vertebral metastases, these usually induced local bone or root pains without causing any cord pressure.

Cranial involvement

There were thirteen cases which presented symptoms and signs due to metastatic deposits in the brain and meninges. In evaluating these symptoms one encounters difficulties which are not met with the more simple and definitive affections of the peripheral nerves. In the first place there can be no doubt that many of the metastases in the cerebrum and cerebellum are entirely latent both because of their small size and their location in clinically silent areas of the brain. Furthermore evidence of increased intracranial pressure which is so valuable a symptom of brain tumor when localizing symptoms are absent, was frequently wanting. We can best portray the varied manifestations of cranial involvement in these patients by giving in condensed form the neurological symptoms which some of them presented:

1. Headache three weeks; Jacksonion attacks in left arm; weakness of left face and arm; left hyperreflexia; choked disc; cerebrospinal fluid pressure 200.

2. Left hemiplegia; somnolence; memory impairment followed by stupor; left hyperreflexia; choked disc.

3. Head injury three months previously; headaches; momentary unconsciousness, nystagmus; Kernig sign; knee and ankle jerks absent; clinical diagnosis, "subarachnoid hemorrhage." Lumbar puncture, xanthochromia; normal pressure; no block; increasing drowsiness and weakness of extremities. Suspected cerebellar tumor.

4. Generalized convulsions and weakness of left arm.

5. Drowsiness and lethargy. Diminished reflexes left side—cerebrospinal fluid pressure normal.

6. Yawning three weeks; two weeks right temporal headache; weakness; somnolence; weakness and numbness of left side of body; blurred vision; choked disc; left Babinski sign; Ventriculogram, posterior horn displaced to left. Left homonymous hemianopsia. Increased cerebrospinal fluid pressure. Probably multiple tumors.

7. Headache six weeks; nausea and vomiting; staggering gait; drowsy; failure of memory;

cerebellar signs; right facial weakness, right arm clumsy; speech disturbance; eye grounds normal; right corneal hypesthesia; internal hydrocephalus; cerebrospinal fluid pressure 130. Right cerebellar and vermis tumors.

8. Occipital headache four weeks; nausea and vomiting; fainting spells; ataxia right arm; Babinski sign; ankle clonus; choked disc; cerebrospinal fluid pressure 107. Multiple cerebral and cerebellar tumors.

These cases illustrate the common features of cranial disease with carcinoma of the lung. In a number of cases the diagnosis remained for a while in doubt, especially when there was not yet awareness of the primary tumor in the lung. It is of interest to note, as is frequently recorded in the literature, that intracranial new growths may exist without any signs of increased pressure as evidenced by the optic disc or lumbar puncture. The symptoms progressed with remarkable rapidity, the whole course of the disease being encompassed within a few weeks. There can be little doubt that hemorrhage into the tumor in one case precipitated the symptoms which had all the clinical characteristics of a subarachnoid hemorrhage.

Intracranial metastases occurred with both the circumscribed and infiltrating types of tumor, proportionately somewhat more frequently in the former. The tumor was situated in the upper lobe in all but two of the cases.

Carcinoma of meninges

We finally record one case which illustrates the selective localization of the tumor in the meninges in which the clinical picture of multiple neuritis was closely simulated. The first symptoms were a loss of power in the lower extremities and facial muscles and difficulty in swallowing. There were absent reflexes, tenderness to pressure of the lower extremities, and tingling of the toes. Paralysis of the left half of the soft palate and left vocal cord was present. Diagnosis at that time was facial diplegia and polyneuritis. The cerebrospinal fluid revealed xanthochromia, increased total protein and low pressure. There was no block. Seven months later there appeared headaches; paresthesia of the upper extremity; incontinence; atrophy of the legs; sensory changes; paralysis of the left internal rectus muscle; partial fifth nerve involvement; bulbar speech; and an absent pharyngeal reflex. At autopsy the spinal cord showed innumerable grape-like tumors along the cauda equina and the origins of the peripheral nerves. The lumbo-sacral plexus and sacral roots were studded with similar tumors. At the base of the brain the cranial nerves were embedded in these tumors which infiltrated the pia mater. The brain and cord itself were not invaded. This patient had a primary carcinoma in the lower lobe of the right lung which throughout the illness was symptomatically silent.

LITERATURE

A cursory survey of the literature discloses numerous instances of central nervous system involvement with carcinoma of the lung. Because these present some features of a unique character, we herewith give some of them in summary. The French literature records a considerable number of such cases, emphasis being constantly placed on the frequency with which the associated lung tumor

was unsuspected. Chartier (3) recites a syndrome resulting from metastases localized to the basilar meninges in which the optic nerve and the third, fourth, fifth, sixth, seventh and twelfth nerves were affected. There was rapid loss of vision, headache, difficulty in speech, right ptosis, right ophthalmoplegia, dilatation of one pupil, corneal anesthesia and paralysis of the facial muscles and of the tongue with atrophy of the latter. Babonneix (4) reports an entirely different group of symptoms due to similar metastases to the basal dura but in a more posterior location. There were signs of vestibular disturbance, deafness, left glossopharyngeal and vocal cord paralysis, also paralysis of the left sternomastoid and trapezius muscles. The ocular fundi were normal and there was no increase in cerebrospinal fluid pressure. Here also the lung tumor was silent.

Roger (5) records a number of cases which, because of the outstanding nature of the nervous symptoms, he describes as "cerebral forms of cancer of the lung." His patients had typical Jacksonion attacks and he emphasizes the complete absence of signs of increased intracranial pressure.

Reichman (6) has an extensive review of this subject and records seven cases of silent pulmonary tumor with a great variety of symptoms due to metastases in the central nervous system, some of which are here summarized:

Case 1. Compression myelitis simulating Landry's paralysis.

Case 2. Sciatic syndrome with metastatic lesion of the twelfth dorsal vertebra.

Case 3. Tabetic syndrome. There were metastases in the sixth to the twelfth dorsal vertebrae and also cerebral metastases and tumors in the dura at the base of the brain. There were unequal pupils, Argyll-Robertson, and ataxia and third nerve paralysis.

Case 4. Typical acute hemiplegia due to cerebral metastases.

Case 5. Slow progressive hemiplegia with tumor of the frontal lobe and vascular thrombosis.

Case 6. Jacksonion attacks with right hemiplegia and sudden death due to a hemorrhage into the tumor.

Paviot (7) describes a most unusual localization of a metastasis in the ciliospinal center of the cord in a case of silent carcinoma of the lung. The patient had headache, vertigo, difficulty in locomotion and spells of unconsciousness with Jacksonion attacks of the leg, also tonic convulsions of an upper extremity and a bilateral Babinski sign. There was bilateral papilledema but a normal cerebrospinal fluid pressure. These symptoms were due to a number of small metastases in the cerebellum. In addition there was a left Horner's syndrome. This was not due, as is usual, to involvement of the cervical sympathetic but resulted from a metastasis in the left half of the cervical cord where it destroyed the antero- and postero-lateral columns including the fibers to the cervical sympathetic.

In this country there are scattered references to the neurological complications of lung cancer. Prominent among these is the report of Parker (8) who has especially commented upon the occurrence of cerebral metastases with latent lung tumors. Globus and Selinsky (9) reported twelve cases of metastatic tumors of the brain, two of which were secondary to a primary lung tumor which was entirely latent. They emphasize the frequent absence of localizing objective

neurological signs. They are impressed by the acute onset of cerebral manifestations commonly of a disseminating character simulating a meningo-encephalitic process. Finally in the German literature in addition to instances of cerebral and spinal metastases, there are a considerable number of cases of dural and arachnoid carcinosis which presented a great variety of symptoms. As long ago as 1902 Seifert (10) recorded such cases, three of which were secondary to pulmonary cancer. These cases of carcinomatous meningitis presented every conceivable symptom, including signs of meningeal irritation with various types of focal symptoms such as Jacksonion attacks, mono- and hemiplegia and profound psychic disturbances. The course was very rapid, often only a few weeks. In other cases there were symptoms of progressive paralysis which were difficult to distinguish from luetic disease of the nervous system. Finally, one form associated with cancerous invasion of the pia about peripheral nerves in the spinal cord, faithfully reproduced the clinical picture of multiple neuritis.

DISCUSSION

The data which we have presented may serve a twofold purpose. From a purely descriptive standpoint the neurological manifestations of lung cancer constitute an important group of symptoms which may appear in the course of a disease which in other respects has many unusual features. The nature and the clinical prominence of the metastases make it possible for carcinoma of the lung to assume strange disguises and to simulate organic disease of many kinds. It has been mistaken for cardiac, hepatic, arthritic, osseous and the most varied pulmonary diseases. This characteristic is nowhere so marked as in the field of neurology. The power of simulating diseases of the nervous system is in no small degree due to an apparent predilection of the cancer cells for nerve tissue; it is aided by the fact that the primary tumor may be entirely latent and may not betray itself by symptoms or physical signs of pulmonary disease.

In the series of cases here reported we have devoted some attention to this feature of carcinoma of the lung. Cough and expectoration are fairly representative symptoms of pulmonary carcinoma. If we use them as an index we have found that neurological signs or symptoms of a significant character either preceded or were simultaneous with pulmonary symptoms in twenty-five cases. In nine of these there were no pulmonary symptoms of any kind throughout the course of the disease. Under these circumstances there was nothing to indicate that the neurological changes were other than primary. Proportionately this tendency toward latency was more pronounced in the circumscribed peripheral tumors. It has therefore happened on a number of occasions that craniotomy was performed for a presumably primary brain tumor which was in fact secondary to an unrecognized carcinoma of the lung. So frequent is this association that it is now common practice for the neurosurgeon before he operates for brain tumor to assure himself by means of a Roentgen examination that the lungs are uninvolved.

In the larger domain of non-surgical diseases of the nervous system, the neurologist must equally be on his guard. A peripheral neuritis, a myelitis, a tabetic

syndrome, an ophthalmoplegia or a meningitis may on investigation prove to be due to metastases from a primary growth in the lung whose symptoms may be so completely latent or so minor in character as to escape attention.

In conclusion it may be pointed out that the neurological complications of lung cancer have especial interest for thoracic surgeons who now attempt the operative removal of these tumors in increasing numbers. It is generally agreed that from a purely surgical standpoint the circumscribed tumors offer the best prospect of successful operative removal. Unfortunately, this prospect is measurably dimmed by the proportionately greater number of neurological complications which are found in this type of tumor compared with the infiltrating form. Thus, of thirty-six cases of circumscribed tumors which presented a good operable outlook, operation was precluded in twenty-three cases because of neurological complications which would have rendered the operation futile. In spite of the gleam of hope which has been shed on the future of these patients by the brilliant feats of the thoracic surgeon, it must be confessed that the neurological complications of cancer of the lung cast a somber shadow over prospects for their cure.

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* A recent paper on Metastatic Tumors of the Brain by Globus, J. H. and Meltzer, T., published in Arch. Neurol. & Psychiat., 48: 163, 1942 shows approximately 50 per cent of their cases to have the lung as the primary source of cerebral metastases.

SOME OBSERVATIONS ON THE RELATIONSHIP OF THE VAGUS NERVE TO PEPTIC ULCER[1]

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INTRODUCTION

The etiology of peptic ulcer is as yet unknown. In recent years the idea that it is a psychosomatic disease has rapidly come to the fore. Whatever the ultimate cause may prove to be, it is nevertheless generally accepted that the immediate mechanism of the lesion is the digestive action of hydrochloric acid and pepsin on the gastric mucosa. Other factors, such as the mucosal susceptibility and mechanical impact are also obviously of importance. However, most observers feel that gastric hypersecretion is the central factor in the problem.

Before discussing the question of this hypersecretion in peptic ulcer, it is necessary to say a few words about the normal mechanism of gastric secretion. Approximately one-half of the secretion after a meal is "nervous" and produced through the vagus nerve. The rest is accounted for by chemical messengers chiefly from the antrum to the fundus glands. This second chemical phase acts without nervous intervention. In the problem of gastric hypersecretion in ulcer, the question has arisen as to whether the increased secretion is nervous or chemical in origin. In this brief presentation, we wish to discuss that question and to point out some of the theoretical and practical implications involved.

STUDIES AND OBSERVATIONS

As a result of many years of study we have arrived at the conclusion that the hypersecretion of ulcer is nervous in origin. Our studies and observations may be summarized as follows:

1. Using special test meals (chewing of an orange for the nervous phase, bouillon injected into the stomach through the Rehfuss tube without the patient's knowledge for the chemical phase), we have found that the nervous phase of gastric secretion is high in ulcer patients, whereas the chemical phase is normal. The chemical phase may even be low in gastric ulcer.

2. Using histamine (a specific stimulus of the chemical phase) we have found only a moderate response in ulcer patients.

3. Using insulin (15 units intravenously produces a marked hypoglycemia which is a powerful stimulant to the vagus nucleus), we have found in some unpublished experiments that ulcer patients respond with a very high secretion as compared with normals.

4. In studying the gastric secretion during the night after a standard supper, it has been found that ulcer patients manifest a high secretion and high acidity during the night whereas normal patients show little or no secretion during the

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night. Professor B. P. Babkin in a careful consideration of the night secretion has concluded that it is of vagal origin.

5. After partial gastrectomy for duodenal ulcer, approximately one-half of the patients continue to secrete free hydrochloric acid. Since the chemical phase has been almost completely removed by the resection of the antrum, this is presumably due to vagal influence. That this is true is proved by the exhibition of atropine and by vagotomy, both of which abolish this postoperative secretion. Since the persistence of the acid occurs only in the cases with a marked preoperative hypersecretion, the role of the vagus nerve in the hypersecretion of duodenal ulcer is apparent.

6. If we accept the psychosomatic theory of the causation of ulcer, it is logical to conceive of the gastric hypersecretion as the result of stimuli over nervous pathways.

7. Sham feeding experiments and also electrical stimulation of minute hypothalamic areas and along the course of the vagus nerve, have produced ulcerations in the stomach and duodenum of experimental animals.

As a result of these studies and considerations, one is strongly impressed by the probability that the secretory disturbances leading to peptic ulcer are brought about through the vagus nerve.

PRACTICAL APPLICATIONS

If one accepts the conclusion that whatever the ultimate cause of ulcer may be, the lesion is actually brought about by the acid-pepsin factor and that this in turn is mediated by the vagus nerve, it seems logical to attack the vagus nerve in therapy. Practically all therapists advocate parasympathetic depressants (chiefly atropine and belladonna) and general nerve sedatives (bromides and phenobarbital).

Various forms of surgical approach to the problem have appeared from time to time. Stierlin practiced an encircling mural incision about the cardia to sever the vagus fibres. Charles Mayo sectioned the vagi at the incisura angularis to lessen pylorospasm. Most authors have stressed the motor factor. It remained for the gastro-intestinal group at this hospital to stress the acid-depressant effect of vagotomy. When it was found that the persistence of free hydrochloric acid in 50 per cent of ulcer patients with partial gastrectomy for duodenal ulcer was probably due to the vagus nerve since atropine completely suppressed this acidity, the late Eugene Klein suggested anterior subphrenic vagotomy in addition to partial gastrectomy in the cases of duodenal ulcer with very high preoperative acidity. He reported the first 10 cases performed by Dr. A. A. Berg, in which a successful postoperative achlorhydria was achieved uniformly. In our experience, postoperative achlorhydria prevents completely a recurrent jejunal ulcer and thus this operation is really a permanent cure of the disease. A few years ago the author with Dr. Berg presented before the American Gastroenterological Association a larger number of cases with a 5 to 10 year follow-up study. The results were as follows:

Thirty-four patients with duodenal ulcer with a very high preoperative acidity

were subjected to the operation of partial gastrectomy with anterior subphrenic vagotomy. 26 developed a postoperative achlorhydria. It was possible to follow-up 31 of these cases for 4 to 9 years. All have remained well. Apparently the vagotomy is harmless.

Because of these splendid results, we advocated very strongly the addition of subphrenic anterior vagotomy to partial gastrectomy in the cases with high preoperative acidity. We have found that without the vagotomy, the recurrences are found practically entirely in the group with high preoperative acidity.

A careful recent study by Doctors S. Mage and Leon Ginzburg has established the fact that gastro-enterostomy heals duodenal ulcer but favors the formation of jejunal ulcer. The recurrent jejunal ulcer is probably due to motor and secretory factors impinging on the susceptible jejunal mucosa. It seems logical to incriminate the vagus nerve in these excessive motor and secretory activities. Therefore, the author a few years ago suggested the procedure of gastro-enterostomy plus anterior subphrenic vagotomy for the treatment of some selected cases of duodenal ulcer. They were chiefly uncomplicated cases with a high nervous secretion. This type of operation has been carried out in 5 cases to date. Two have been followed up for several years, 1 for 3 years, and 2 for 2 years. All have remained well without recurrences. Acidity studies revealed a temporary lowering of the acidity in some and permanent in others. These cases are being published in detail elsewhere. Emphasis should be placed on the idea that this operation should not replace the operation of partial gastrectomy which is indicated for the severe, complicated ulcers. It seems definitely contraindicated in pyloric obstructions with atony since vagotomy definitely diminishes gastric tone and peristalsis. That is probably the reason for the failure of vagotomy alone (unilateral or bilateral) to relieve ulcer or functional cases. Such a procedure in the intact stomach leads to a distressing atony with many untoward symptoms. That is also the reason that anterior subphrenic vagotomy and not both anterior and posterior vagotomy has been advocated by us. The routine of adding this procedure to both partial gastrectomy and gastro-enterostomy is really to lessen the nervous phase of gastric secretion. Stomal regurgitation plus the removal of large areas of the ulcerative gastritis together with the usual new postoperative gastritis are all also important in lessening the postoperative acidity. The vagotomy is merely an important accessory factor and in most cases is sufficient to induce the desired achlorhydria.

In general, it may be concluded that the addition of anterior subphrenic vagotomy is a harmless procedure, and in the majority of cases studied leads to that *sine qua non* of ulcer healing and lack of recurrences, viz., achlorhydria. In our experience, it does not matter if the achlorhydria is a true one or an apparent (neutralization) one. In either case, recurrences have not been seen. The procedure is technically simple and adds but a few minutes to the operative time. For all of these reasons we advocate vagotomy in the surgical therapy of duodenal ulcer. In gastric ulcer it is not needed since partial gastrectomy alone produces postoperative achlorhydria in practically 100 per cent of the cases.

Unfortunately the clinical tests in use today do not permit us to make an ac-

curate study of the effect of anterior subphrenic vagotomy on the nervous phase of gastric secretion. As yet, we can only study its effect on the usual fractional secretory curve. We cannot estimate the effect on the amount of secretion nor can we study the effect on the nervous phase separately. The reason is not only the complexity and number of factors involved, but also the lack of a suitable test procedure. Some studies, using color dilution indicators for the amount of secretion and insulin as a test for "vagality" (vagus nerve stimulation), are being carried out in our Gastro-Intestinal Physiology Laboratory by Franklin Hollander and may soon be available for use in the clinical study of this problem. The entire problem of the study and utilization of the procedure of vagotomy is being attacked again on the surgical service of Dr. Ralph Colp.

CONCLUSION

1. Peptic ulcer is probably a psychosomatic disease.
2. The lesion, *per se*, is brought about by excessive acid-pepsin secretion acting on a susceptible mucosa.
3. Evidence is cited to prove that the hypersecretion and hyperchlorhydria is due to the vagus nerve.
4. Both medical and surgical attack on the vagus nerve is desirable in the therapy of peptic ulcer.
5. Bilateral vagotomy alone is unsuccessful in the treatment of peptic ulcer and is actually contra-indicated.
6. Anterior subphrenic vagotomy plus partial gastrectomy is advocated in the treatment of duodenal ulcer with hypersecretion.
7. Anterior subphrenic vagotomy plus gastro-enterostomy is advocated in the treatment of some selected cases of uncomplicated duodenal ulcer.
8. Because of the lowered acidity and good clinical results these procedures are strongly advocated in the surgical treatment of duodenal ulcer.

HEADACHE MECHANISMS[1]

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During the last ten years attempts have been made in this clinic to acquire information as to the nature and mechanism of headache. The purpose of this communication is to bring together the evidence so far adduced about this topic. It is an honor to be able to dedicate a resumé of this work to Dr. Bernard Sachs.

Pain sensitive structures of the head. The sensitivity to pain of the tissues covering the cranium, the cranium itself, and most of the intracranial structures, has been ascertained from a series of patients during surgical procedures on the head. Some of the "pain pathways" and the mechanisms of headache are defined.

The use of a variety of stimuli has resulted in the following conclusions about the sensitivity to pain of the structures investigated:

1. Of the tissues covering the cranium, all are more or less sensitive to pain, the arteries being especially so.

2. Of the intracranial structures, the great venous sinuses and their venous tributaries from the surface of the brain, parts of the dura at the base, the dural arteries and the cerebral arteries at the base of the brain, the fifth, ninth and tenth cranial nerves, and the upper three cervical nerves, are sensitive to pain.

3. The cranium (including the diploic and emissary veins), the parenchyma of the brain, most of the dura, most of the pia-arachnoid, the ependymal lining of the ventricles and the choroid plexuses, are not sensitive to pain.

With the exception of those sensations that resulted from stimulation of the parenchyma and cranial nerves, the only sensation that was experienced on stimulation of the intracranial structures was pain.

Stimulation of the pain sensitive intracranial structures on or above the superior surface of the tentorium cerebelli resulted in pain in various regions in front of a line drawn vertically from the ears across the top of the head. The pathways for this pain are contained in the fifth cranial nerve.

Stimulation of the pain sensitive intracranial structures on or below the inferior surface of the tentorium cerebelli resulted in pain in various regions behind the line just described. The pathways for this pain are contained chiefly in the ninth and tenth cranial nerves and the upper three cervical nerves.

From the data available, six basic mechanisms of headache from intracranial sources have been formulated. Headache may result from 1) traction on the veins that pass to the venous sinuses from the surface of the brain and displacement of the great venous sinuses; 2) traction on the middle meningeal arteries; 3) traction on the large arteries at the base of the brain and their main branches; 4) distention and dilatation of intracranial arteries; 5) inflammation in or about

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any of the pain sensitive structures of the head, and 6) direct pressure by tumors on the cranial and cervical nerves containing many pain afferent fibers from the head.

Intracranial diseases commonly cause headache through more than one of these mechanisms and by involvement of more than one pain sensitive structure. Traction, displacement, distention and inflammation of cranial vascular structures are chiefly responsible for headache.

Headache from intracranial disease is usually referred pain. Local tenderness of the scalp may serve as an index to the structures responsible when a lesion produces direct irritation of pain sensitive structures. Disease of remotely separated pain sensitive structures may cause pain and hyperalgesia in identical areas.

Headache associated with changes in intracranial pressure. The headache so frequently associated with abnormally high or low cerebrospinal fluid pressure has long been the subject of contradictory speculations. In a study of headache associated with changes in intracranial pressure, relevant factors were analysed as follows: In normal human subjects, headache was induced by drainage of cerebrospinal fluid through a lumbar needle. Studies of headache and spinal manometrics during shifts in position on a tilt-table showed:

1) With the subject erect headaches were regularly induced by removal of 15 to 18 cc. of fluid (1 to 1.2 per cent of total intracranio-spinal contents).

2) Such headache responded quickly and directly to changes in angle of tilt, jugular compression, or restoration of normal intracranial fluid volume, measures which altered the amount of traction by the brain on anchoring structures. In these responses the headache was shown to be relatively independent of intracranial pressure.

3) Abnormally high intracranial pressures were produced by intrathecal injection of saline, but without headache at any time.

From these data it is concluded that headache associated with altered intracranial pressure, whether the pressure be high or low, involves the same primary mechanism, namely, traction on pain sensitive intracranial structures, and that generalized increase or decrease in pressure is only a contributory rather than an essential or sole factor.

Brain tumor headache. That increased intracranial pressure is not the dominant factor in headache associated with brain tumor was suggested by an analysis of 72 patients:

1) Headache occurred almost as commonly (82 per cent) in 23 patients without increased intracranial pressure as it did (94 per cent) in 49 patients with increased pressure.

2) The reduction of elevated pressure did not inevitably eliminate tumor headache.

3) At surgical operation the headache could be reproduced experimentally by distortion of pain sensitive structures adjacent to the tumor.

Brain tumor headache is produced by traction upon intracranial pain sensitive structures, chiefly the large arteries, veins and venous sinuses, and certain cranial

nerves. There are two types of traction which operate singly or in combination: local traction by the tumor upon adjacent structures; and distant traction by extensive displacement of the brain, either directly by the tumor, or indirectly by ventricular obstruction (internal hydrocephalus).

As an aid in the localization of brain tumor, the value of headache is limited by two facts: the headache may be remote from the site of its production and the site of production of the headache may be remote from the tumor.

In spite of these limitations, when it is interpreted in terms of known principles of intracranial pain production and pain reference, the headache of brain tumor may significantly aid in the diagnosis and localization of the lesion.

From these studies the following generalizations concerning brain tumor headache as an aid to localization seem justified.

1) Although the headache of brain tumor is often referred from a distant intracranial source, it approximately overlies the tumor in about one-third of all patients.

2) Brain tumor headache in the absence of papilledema is of great localizing value. In about two-thirds of such patients the headache immediately overlies or is near the tumor and in all when unilateral, it is on the same side as the tumor.

3) Headache is almost always present with posterior fossa tumor.

4) Headache may be absent with any of the common types of supratentorial tumor.

5) The headache of posterior fossa tumor is almost always over the back of the head, although it may occur elsewhere as well.

6) Headache is usually the first symptom of posterior fossa tumor except in cerebello-pontile angle tumors.

7) Headache is the first symptom of one-third of supratentorial tumors.

8) The headache of cerebello-pontine angle tumors is frequently and sometimes solely post-auricular.

9) Headache from supratentorial tumors is rarely in the back of the head unless associated with papilledema.

10) When supratentorial tumors cause headache in the back of the head, headache in the front of the head is usually also present.

11) When headache is both frontal and occipital it indicates extensive displacement of the brain and has little localizing value.

12) Brain tumor headache is usually intermittent, but when it is continuous its value in localization is greatly enhanced.

Histamine headache. The association of headache following intravenous histamine injection with increase in the amplitude of the intracranial pulsations was photographically demonstrated. Simultaneous records of the systemic arterial blood pressure, the cerebrospinal fluid pressure, the temporal artery pulsations and the intracranial pulsations were made. The demonstrated correlation is taken as further evidence that the histamine headache is primarily due to dilatation and stretching of the pial and dural arteries and their surrounding tissues.

Such histamine headaches were abolished by increasing the intracranial pres-

sure, thereby giving extramural support to the cerebral arteries at the base of the brain. This is further evidence that histamine headaches result mainly from the dilatation and distention of cerebral arteries.

Histamine headache does not depend upon the integrity of sensation from the superficial tissues. The extracranial and dural arteries play a minor role in contributing to the pain of histamine headache. Cerebral arteries, principally the large arteries at the base of the brain, including the internal carotid, the vertebral and the basilar artery and the proximal segments of their main branches, are chiefly responsible for the quality and intensity of histamine headache. Although there may be other less important afferent pathways for the conduction of impulses interpreted as headache following injection of histamine, a) the fifth cranial nerve on each side is the principal afferent pathway for headache resulting from dilatation of the supratentorial cerebral arteries and felt in the fronto-tempero-parietal region of the head, and b) the ninth and tenth cranial and upper cervical nerves are the most important afferent pathways for headache resulting from dilatation of the arteries of the posterior fossa and felt in the occipital region of the head.

Headache associated with fever. Observations of the amplitude of pulsations of the cranial arteries during headache associated with experimentally induced fever showed that the spontaneous increase and decrease of the intensity of the headache paralleled the changes in amplitude of pulsations of these arteries.

A similarity between the pyrexial and the histamine headache was that the amplitude of pulsations of the cerebrospinal fluid in both types of headache was greatly increased, in contrast to migraine headache, which was not accompanied by any such increase in amplitude of cerebrospinal fluid pulsations. The observation was made, moreover, that increasing the cerebrospinal fluid pressure in the subarachnoid space relieved fever headache (Pickering).

The fact that increasing the intracranial pressure decreased the intensity of the headache indicates that the mechanism of the headache in fever and that of the headache following injection of histamine are similar, and that, in both, the intracranial arteries are the chief contributors to the pain. It is likely that the headache associated with acute infections, sepsis and bacteremia are similarly due primarily to the distention of intracranial arteries.

Migraine headache. Changes in the intensity of the migraine headache are related to changes in the amplitude of pulsations of the cranial arteries, chiefly the branches of the external carotid arteries. Factors which decrease the amplitude of pulsations decrease the intensity of the headache. Thus, it has also been shown by means of observations and photographs, made both before and during the action of ergotamine tartrate, that this agent reduces the amplitude of pulsations of the aforementioned arteries by about 50 per cent, and thereby diminishes the intensity of or terminates the migraine headache. Reduction in the amplitude of pulsations of the temporal artery by digital pressure on the carotid artery on the affected side is accompanied by reduction in the intensity of the headache. The constriction of the branches of the external carotid artery both superficial and dural results in relief of migraine headache. Conversely,

experimental distention of the temporal artery, by increasing the intravascular pressure, results in pain.

Therefore, the headache of migraine is produced by distention of cranial arteries, chiefly, but not exclusively, the branches of the external carotid, and procedures that constrict the cranial arteries and thus reduce their amplitude of pulsation will diminish or terminate the headache.

The role of the pial and cerebral arteries in the migraine headache needs further definition. It should be recalled that faradic stimulation of the proximal few centimeters of the anterior, middle and posterior cerebral arteries and the first few centimeters of the intracranial portion of the internal carotid artery causes pain within, behind, or over the homolateral eye. Furthermore, stimulation of the vertebral and basilar arteries and the proximal portions of their branches causes pain in the occipital and suboccipital region. These areas are commonly involved in migraine attacks. The evidence from persons who have migraine headache that headache induced by histamine resembles the most intense migraine headache suggests that the larger arteries of the base of the brain and their immediate branches may be implicated in some patients during severe migraine headache.

On the other hand, there is considerable evidence against the view that the headache is due primarily to dilatation of the dural and cerebral arteries. Raising the cerebrospinal fluid pressure which dampens the pulsations of these vessels, would diminish the headache, as in the case of the headache induced by histamine. Since not even the worst attacks of migraine headache are reduced in intensity by raising the cerebrospinal fluid pressure as high as 800 mm. of water by means of a manometer system attached to a needle in the lumbar sac, it is indicated that the pial and cerebral arteries are not the major contributors to the pain.

The internal and external carotid arteries and the vertebral arteries have branches both in the subcutaneous tissue and in the meninges. The branches of the external carotid artery predominate numerically both superficially and on the dura. On the other hand, the anterior meningeal artery arises from branches of the internal carotid artery, as do the superficial frontal and the supraorbital artery. Since the area supplied by the latter structures is commonly involved in migraine headaches, branches of the internal carotid artery may contribute to the pain. It is obvious, therefore, that it would be arbitrary to contrast these arteries too sharply.

Although most attacks of migraine headache are limited to the temporal, the frontal or the occipital region, some patients have pain elsewhere. In the face, below the eye and behind and below the zygoma, severe throbbing pain, which seems to emanate from the back teeth of the upper jaw, occasionally occurs. Another variant is facial pain, which spreads behind the angle of the jaw, down the neck and into the shoulder. The latter aching sensations are sometimes associated with awareness of unusual throbbing in the neck.

The pains described can and probably do result from dilatation and distention of the extracranial portion of the middle meningeal artery, between its origin and

the point of entrance into the skull, the internal maxillary artery and the trunks of the external and the common carotid artery. It has been shown that the latter structures are sensitive to pain, and the sites in which pain is felt are the face, neck, and shoulder.

It is likely, therefore, that for the histamine headache, the cerebral branches of the internal carotid, basilar and vertebral arteries at the base of the brain are primarily responsible. To the migraine headache, however, the extracranial, and possibly the dural, branches of the external carotid artery are the chief contributors.

Mechanism of scotomas associated with migraine headache. To ascertain whether dysfunction of the cerebral vasculature is responsible for the pre-headache symptom of scotoma, a vasodilator agent, amyl nitrite, known to affect cerebral vessels, was employed. It is justifiable to infer that cerebral vasodilatation induced without a fall in blood pressure increases cerebral blood flow, whereas a sharp drop in blood pressure, regardless of the state of the cerebral arteries, decreases the cerebral blood flow. Symptoms due to cerebral vasoconstriction should be overcome by cerebral vasodilatation in the presence of a sustained normal level of blood pressure, but they should be augmented by a fall in blood pressure with accompanying decrease in cerebral blood flow. Experiments based on these two potential actions of the vasodilator drug amyl nitrite were performed by a subject having pre-headache scotomas, who was skillful in observing his own visual fields.

It was apparent from such experiments that cerebral vasodilatation associated with a sustained normal level of blood pressure caused symptoms to disappear, whereas a procedure that decreased cerebral blood flow caused the symptom to become worse. From this it may be deduced that cerebral vasoconstriction was responsible for the visual defect in this patient with migraine. It is also likely that the cause of the visual defect was not in the retina or orbit, but within the cranial cavity.

Headache associated with hypertension. Studies made of the headache associated with hypertension have revealed that essentially the same mechanism is operative in producing this pain as in producing the migraine headache. It is to be emphasized that this statement applies not to the so-called hypertensive encephalopathy of Fishberg, or "hypertensive crisis," but rather to the frequent, severe and often incapacitating headaches suffered by hypertensive patients who may otherwise be free of symptoms. The term "hypertensive headache" is misleading, since it implies that the frequency and severity of the headache are directly related to the level of the blood pressure.

Almost all the patients with hypertension and associated headaches in this series had had headaches for many years. In numerous instances the headache was known to have preceded the onset of the hypertension and, in some patients, changed only in intensity with the rise in blood pressure.

The following data indicate that the pial and cerebral arteries are not the prime contributors to the headache, and that the headache associated with hypertension, like that of migraine, arises chiefly from the dilatation and dis-

tention of certain branches of the external carotid artery: 1) The headache was not relieved by increasing the cerebrospinal fluid pressure. 2) There was no increase in the amplitude of pulsations of the intracranial arteries during the headache, and the amplitude of pulsations of these arteries did not become less as the headache diminished in intensity. 3) Ergotamine tartrate, which in the head acts chiefly on the branches of the external carotid artery, reduced the intensity of the headache. 4) Manual pressure on the temporal, frontal, supraorbital, postauricular, or occipital artery decreased or abolished the headache. 5) Ligation of the middle meningeal or the temporal artery, especially the latter, decreased the intensity of the headache for some months.

That the headache in subjects with hypertension bears no direct relationship to the level of blood pressure or pulse pressure has been previously observed. The headache may be present when the blood pressure is relatively high, moderate or low. By pressing the thumb upon the common carotid artery the intensity of the headache is reduced, with an accompanying decline in the amplitude of pulsations. Decrease in the intensity of headache in the temporal region followed similar pressure upon the corresponding temporal artery. Furthermore, when ergotamine tartrate did succeed in appreciably decreasing the amplitude of pulsations of the cranial arteries for a shorter or longer period, intensity of the "hypertensive" headache decreased despite the fact that the ergotamine tartrate considerably increased the already elevated systolic and diastolic pressures. If little or no reduction of the amplitude of pulsation of the arteries occurred there was no reduction in the intensity of the headache. Hence, headache with hypertension likewise is influenced by agents that decrease the amplitude of pulsations of the cranial arteries.

This view is illustrated further by the following subject who was intensively investigated. A man with hypertension had incapacitating headaches every morning, chiefly on the right side. After an adequately long preliminary period of recording the intensity and frequency, the right middle meningeal artery was ligated. Following this procedure the daily headache on the operated side was reduced to about a half or less of its former intensity. About a month later the right temporal artery, carefully avoided in the first operation, was ligated. This procedure was followed by almost complete freedom from headache on the right side. Less intense headaches, though present before, were now more troublesome over the left eye and temple. Hence, about a month later the left temporal artery was similarly ligated. During the subsequent two months no headache was experienced in either right or left temporal region. Such headache as occurred, which was approximately one-third as intense as previously, was now localized in the region immediately over both eyes and in the midline. Throughout these procedures the levels of systolic and diastolic blood pressures did not vary appreciably and such changes as took place bore no direct relationship to the intensity of the headache. These observations indicate the intimate relationship between headache associated with hypertension and the cranial arteries.

The fact that the high level of blood pressure among hypertensive subjects is not a sufficient condition for headache does not justify the assumption that these

phenomena are unrelated. Indeed, this, too, would be contradicted by the facts of common experience, since some persons with hypertension never had headache until the hypertension became established. It seems reasonable to postulate that a cranial artery only slightly relaxed for whatever reason would not distend as much, and possibly not to the point of producing pain, if the blood pressure were low. If, however, the sustained level were raised, distention would be greater and therefore pain might readily follow. In other words, a degree of change in the contractile state of the arterial wall, compatible with comfort when blood pressure is average, would be associated with pain when the blood pressure is elevated.

This conception is supported by analogy with experimental evidence on histamine headache. The headache and maximal distention of the cranial arteries occur not immediately after the injection of histamine, when the effect on the contractile state of these vessels is greatest, but some time later, when the blood pressure returns to its initial level. It is at this time that the walls of the cranial artery react to the mounting pressure and headache becomes associated with a level of blood pressure which is ordinarily associated with comfort. The relaxation of arterial walls is thus seen to be one necessary factor in the production of histamine headache, and the level of the blood pressure the other. The analogy to the circumstances in hypertension is close. During an average or normal contractile state of the arterial walls, distention does not occur, and, correspondingly, there is no headache; but should this contractile state be impaired, as by stress, fatigue, or other condition, distention and headache follow. In brief, high blood pressure is a necessary, but not a sufficient condition for this type of headache. There is a significant relation between headache associated with hypertension and the contractile state of the cranial arteries.

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THE DOCTOR PRESCRIBES

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[*New York City*]

The great physicians have always been humanists with a broad knowledge of both literature and science, and to this host belongs our own Bernard Sachs. He has devoted his life and energies to the demonstration that anatomical, clinical, biophysical and biochemical methods must be blended if we are to attain an understanding of the life of the body. It has always been his contention that though medicine cannot dispense with the assistance of the more exact sciences—it transcends them all.

Even if we had a complete record of all the biochemical and biophysical processes that occur when a swallow returns from Yucatan to the place of its birth in a New Jersey farmstead, we should not understand the bird's remarkable homecoming. The organism transcends mechanism and is a "historic being."

There is a remarkable inter-relationship between mind and body—described for centuries by the poets, of which we have been able only recently to know the "scientific" basis, in small part. For example, we know that anger stimulates the production of adrenalin. But why "dyspepsia warps the judgment and dulls good feeling," or why "a merry heart is the life of the flesh and good news promotes digestion" remain as yet biochemical secrets—soon to be fathomed, we hope, by the psychosomaticists! Mind and body, subjective and objective, are so closely intertwined that most physicians know their science is really psychobiology. Likewise, in sociology, the biological foundations cannot be ignored without great loss. There is a social aspect of heredity, of sex, of multiplication, and of nutrition. There can be no sound medicine that does not keep continually in view the three sides of the triangle—Organism, Functioning, and Environment.

Physicians must not make the error of considering Biological laws as being restricted solely to text books of Biology. The large accumulation of literature, whether prose or poetry, contains data of the practical workings of the Biological Laws of Man and his environment—many more data than any modern "scientific" text could embody.

Let me take this opportunity to write a word on a too often forgotten branch of Therapeutic Medicine. I refer to the method of changing the environment of the patient by means of literature. Let us consider the art and science of the prescription of literature. Too often we are apt to forget the value of literature and the arts—in the modern maze and bustle of chemical test tubes, electroencephalograms, hematocrits and vitamins. I suspect that the books of the Bible and the works of Shakespeare contain more ultimate psycho-biological truths than any test tubes or any ultra-microscope ever will reveal.

Often it becomes the duty of the physician to prescribe, not a pill or a purgative, but an essay or a poem. We physicians must always be adding these literary medicaments to our pharmacy. It is often as important as sulfapyra-

dine—and (I'll safely add) always more pleasant to take! Moreover, the prescription of literature requires much skill in its compounding, for it would not be wise to bring Mrs. Gaskell's "Bronte Family" to those afflicted with tuberculosis, because the volume is a pathetic biography of six children perishing from tuberculosis. On the other hand, the story of the lives of Voltaire, Ruskin, Emerson, and Helen Keller, who lived to advanced ages and achieved much in spite of tuberculosis or other disabilities is encouraging. "The Outermost House" by Henry Beston is a wonderful story of how one man used his lonely convalescence in a most unusual constructive fashion to learn about natural phenomena.

Let us not forget that the title "Doctor" was originally given to teachers of the liberal arts and was first employed in the modern sense by Giles de Corbeil to denote the Salernitan masters, who combined medical knowledge with a flair for poetry. The word *physician* is derived from the Greek meaning *nature*. Gardner pointed out that unfortunately we have become designated by the tools of the art (drugs) rather than by the word "medicus" which in its original interpretation meant "healing."

In "Pygmalion, or the Doctor of the Future," Wilson envisions a great reaction in favor of the doctor, in the older sense of that much abused term. He believes the physician will be a humanist, a lover of the arts as well as a student of the sciences, with the widest possible understanding of human motives. He will be a cultured man with outstanding sympathy. Of what good are the most scientific physicians if they know all precise things, but have no human sympathy or understanding?

The physician cannot create intellect but he can guide it and widen its range. To accomplish this, the physician must familiarize himself with the literary tastes of his patients. This is especially true of convalescing or chronically ill patients. In the periodical-ridden, fidgety world of today a long illness may give a man the first chance in his life for leisurely reading and thinking. Many of our modern super-specialists would be better physicians if they read non-medical literature, in addition to the very latest wrinkles in their own fields. It is a sorry fact of modern life that as the world becomes smaller, competition becomes keener, and the time allotted for liberal pleasures or studies becomes correspondingly shorter. Physicians, like the rest of mankind, find themselves, often of necessity, restricting their learning to a smaller and smaller field—so that the well-known definition of a specialist as "a man who knows more and more about less and less" becomes only too true. The scientist, and certainly the physician, must guard against this. George Bernard Shaw was not joking when he said that "every profession is a conspiracy against the public." We doctors would not be less suspected of such tendencies if we gave our pills with poetry, but we'd be a happier profession if we saw ourselves in historic perspective and if our patients could do likewise.

The sick room is a college of liberal arts. For the sick person the healing effect of suitable literature is of importance. Dr. Johnson's formula that all reading should be for pleasure is doubly true for the sick; and in the vast storehouse of

the world's literature there are books that will give this pleasure to every kind of mind. Different men will need different books. The task of determining the patient's temperament and then prescribing a suitable book should be one important aim of the physician.

We all know that some people are emotionally upset by some subjects out of all proportion to their ordinary importance. For example, if your patient feels too strongly about the Church, it would be better not to hand him the ecclesiastical essays of Thomas Paine on the "Age of Reason"; if he feels too strongly about the war debts, it would be better not to give him Schacht's "The End of Reparations" or Miller's "You Can't Do Business with Hitler" to read; if he's a nervous, exhausted, scared, recently immigrated Austrian Jew, don't give him Hitler's "Mein Kampf." If he's a rabid isolationist (God Forbid!) he probably doesn't like reading at all!

The Bible has always been, and still is the greatest book for the solace of the sick. The renovated volume of the "Bible Meant to Be Read as Living Literature" is a most exciting and readable version of the Good Book.

Biography always makes most satisfying reading. There is nothing so supporting as to read about the struggles and triumphs of successful people. Grimm's "Life of Michael Angelo," James Laver's "Life of Whistler," and Vallery Radot's "Life of Pasteur" are inspiring. Convalescent hemiplegic patients are thrilled to learn that Pasteur triumphed in early life in spite of an attack of apoplexy. I might add Froud's "Lord Beaconsfield," Lytton Strachey's "Eminent Victorians," E. T. Cook's "Florence Nightingale," Freeman's "R. E. Lee," Sandberg's "Abraham Lincoln" and others of a similar nature.

For those interested in music, may I suggest Romain Rolland's "Beethoven the Creator," Newman Flower's "Franz Schubert," Hussey's "Life of Mozart," and Van Loon's "The Arts."

For the patient who loves poetry there is no problem at all; the state of mind which one must bring to the perusal of Spencer or Marlowe, Kipling, Coleridge, Bridges or Masefield is in itself sublimely calm, and the verse of these men will not disturb it.

Mr. Mencken and Mr. Fowler also at one time advised bored Americans to take up science as a hobby. This is a sound plan, if one enlarges the realms of science reading to include archeology, the history of language, etc. The writings of the famous Egyptologist, Flinders Petrie, read like detective stories. The histories of the derivation of words are real treasure hunts. Frazier's "Golden Bough" and his "Folk Lore in the Old Testament" are of never ending interest.

The field of Nature literature offers an immense variety of interest. It extends from learning about the communistic activities of ants to Eddington's "Nature of the Physical World," or the recent mysteries of electrocuting the electron.

Many people may enjoy short stories. The adventures of travel take one's mind off personal physical infirmity. The books of Conrad or the shorter stories of the National Geographic Magazine are magic carpets that instantly remove the sick person from the confines of invalidism. The Reader's Digest

Review is an excellent compilation of abstracts of short stories or articles. For many, the various "anthologies," "readers," and "bedside books" are helpful. This has resulted from a demand for a kind of writing which is suited to overtired bodies and minds. The worker at the end of the day's toil may derive some contentment from a story which carries him as far as the next automobile advertisement and makes no demands on anything but his eyes. Our present day picture magazines give people short visual occipital lobe memory intelligence, and too often let the frontal lobes rot and decay! The short story is a most valuable antidote. Excellent pieces may be found in the writings of Poe, Chekov, O.Henry, Maupassant, and of the recent authors, Irwin Cobb, Don Marquis, and Ring Lardner.

For the person who wants funny stories, any by P. G. Wodehouse or "Nonesense Novels" by Stephen Leacock are sure strikes. And again the detective stories of Milne, Chesterton and Doyle make for complete relaxation. Lord Birkenhead's "Famous Trials of History" are exciting reading. Book collections of Peter Arno's cartoons are poignant exposes of endearing human weaknesses.

Out of professional habit, one might recommend the writings of some literary physicians, notably Maimonnides, Rabelais, Oliver Goldsmith, Keats, Thomas Brown, Robert Bridges, Oliver Wendell Holmes, Somerset Maugham and A. J. Cronin.

Most people will do best on a mixed diet of literature and other vitamins free from the dangers of boredom. A review course in literature, both classical and modern, would well be added to our first courses in therapeutics.

May I remind you of the well-known lines of Colton: "Literature has her quacks no less than medicine, and they are divided into two classes, those who have erudition without genius, and those who have volubility without depth; we shall get second hand sense from the one and original nonsense from the other."

Both science and humanism are necessary to cure disease. The best physician is he who can combine the two, to compound the perfect prescription for each patient.

CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

Presented February 7, 1940

Fibrotic Contracted Bladder due to Chronic Gonorrheal Infection. Bilateral Hydronephrotic Contracted Kidneys

[*From the Surgical Service of Dr. A. Hyman*]

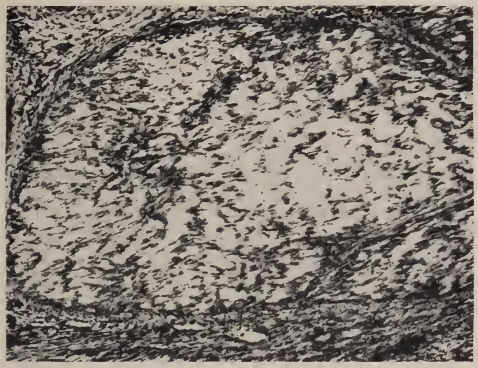
History. (Adm. 445785; P.M. 11328.) This colored man first entered the hospital September 25, 1933 at the age of 30 because of painful joints precipitated by excessive walking. He had previously had three attacks of gonorrhea, the last one having occurred three years prior to entry; since then he had had a chronic morning discharge. The onset of joint pains was attended by headache, fever and chills. The involved joints were the ankles and right elbow. The heart appeared enlarged to percussion. The blood pressure was 140 systolic and 96 diastolic. The urine showed a trace of albumin. The urea nitrogen was 14 mg. per cent. The Wassermann reaction was reported to be 3 plus. Gonococcus complement-fixation was negative. The fever and joint involvement subsided spontaneously within a week. He was started on anti-luetic therapy in the form of iodides and bismuth and discharged on October 5, 1933 for follow-up therapy.

Second Admission. He had failed to report for any treatment during the subsequent three years. His second entry on December 17, 1936 was due to abdominal complaints. For several months he had been belching and passing much flatus. There was an attack of dysuria and frequency of urination three weeks before admission. Two weeks before admission he had a severe attack of diarrhea lasting two days. Ten days later he noted dull persistent right lower quadrant pain, but no vomiting or anorexia. On examination, there was tenderness in the right lower quadrant, rebound tenderness and spasm. The temperature was 102.8 F. The urine examination was negative. An appendectomy was performed through a right McBurney incision. The appendix appeared inflamed, as if by a peri-appendicitis. The terminal ileum was edematous and thickened. The mesentery contained numerous small hemorrhages. This pathology extended up the ileum for 16 inches and then stopped abruptly. The pathologic report of the appendix was chronic appendicitis, which was not significant. His course was uneventful. The possibility of a regional ileitis was considered. Wassermann reactions on the blood and cerebrospinal fluid were completely negative.

Third Admission. At the time of his third admission on September 13, 1936 he was 36 years of age. For three years he had experienced occasional burning on urination, dribbling and difficulty in starting the stream. Four days ago he began to have fever, chills, pain in both sides of the abdomen radiating to the flanks, and the right testicle. There was a marked increase in dysuria and nocturia. He had felt drowsy and sweated profusely.

Examination. He now appeared to be acutely ill. The tongue was coated. The heart was not enlarged; blowing apical and pulmonic systolic murmurs were heard. The blood pressure was 120 systolic and 70 diastolic. The temperature was 103.6°F. There was marked tenderness in both flanks and costovertebral angles. The prostate was smooth, moderately enlarged and tender.

Laboratory Data. Blood: Hemoglobin, 75 per cent; white blood cells 15,700 with 83 per cent polymorphonuclear leucocytes; sedimentation time, 12 minutes; urea nitrogen, 50 mg. per cent; carbon dioxide combining power, 37 volumes per cent. Blood culture, negative. Blood Wasserman reaction, negative; Kahn reaction, plus-minus. Urine: cloudy, alkaline, contained 2 plus albumin and was loaded with clumped white blood cells. Urine culture, B. coli. X-ray examination of the chest was negative. Flat plate of the abdomen showed moderate enlargement of both renal shadows with obliteration of the psoas margin on the right, the findings being compatible with bilateral hydronephrosis. Cerebrospinal fluid: globulin, plus-minus; Wassermann reaction, negative; colloidal gold, 222111000; cell count, normal; dynamics, normal. A smear of the urethral discharge showed numerous intra- and extra-cellular gram negative diplococci.



Section through bladder wall showing replacement of muscles by dense collagenous bundles

Course. Voiding was extremely difficult. Catheterization was performed and revealed a residual of 750 cc. of foul-smelling, badly infected urine. The catheter was, therefore, left indwelling. He was given sulfanilamide, his temperature receded to normal within a week, and the signs of acute renal involvement abated. A residual urine up to 600 cc. persisted. Two weeks later his temperature again rose to 104°F., but because of the development of a marked secondary anemia (hemoglobin 50 per cent) it was felt inadvisable to repeat the course of sulfanilamide. The blood nitrogen urea was still up to 40 to 46 mg. per cent. He was given intravenous fluids and two blood transfusions. Bladder irrigations with acroflavine were also instituted. Cystoscopy showed no definite prostatic obstruction; there was no urethral stricture. The bladder showed evidence of a cystitis. Cystometric readings were normal. Neurological examination revealed no evidence of abnormality of the central nervous system. Intravenous pyelogram now showed definitely hydronephrotic kidneys bilaterally. A transurethral attempt at ureteral catheterization was unsuccessful since the right ureteral orifice could not be visualized, and the left ureteral catheter was caught in a mucosal fold 1 cm. above the orifice.

It was difficult to explain the persistent residual urine, in view of 1) the inability to

demonstrate any obstruction; 2) the normal neurological status; and 3) a normal cystometric determination. Furthermore, even though he was apparently voiding well through the catheter, his blood urea nitrogen, for the most part, remained well above normal limits, accompanied by a persistent acidosis.

Because of continued inability to void spontaneously, recurrent bouts of fever, and hydronephrotic upper urinary tracts, suprapubic cystotomy was performed. Although his temperature became normal thereafter, his condition steadily deteriorated and the blood urea nitrogen rose to 60 mg. per cent. In a final effort to combat the rising blood urea nitrogen, a left nephrostomy was done. The patient never fully recovered from the anesthesia. He remained stuporous, then became comatose and died twenty-four hours later.

Necropsy Findings. The *urethra* was smooth and patent throughout. The *bladder* was markedly contracted. The bladder mucosa was white and thickened. The submucosa and muscularis were strikingly thickened and the musculature infiltrated and replaced by fibrous tissue. There was bilateral uretero- and hydronephrosis. The recent left nephrostomy was surrounded by marked hemorrhage. Enlargement of the regional *lymph nodes* was noted. Chronic infection and fibrosis were seen in the *epididymis*, *prostate* and *seminal vesicles*. On microscopic examination the bladder epithelium showed squamous metaplasia and the musculature conspicuously reduced and substituted by bundles of collagenous tissue. Gram negative intracellular diplococci were still to be seen in smears of the seminal vesicles.

Comment. Dr. Klemperer. The picture of the bladder fits the diagnosis of fibrosing chronic cystitis—an end result of chronic cystitis wherein not only the mucosa and submucosa are involved, but the muscularis shows advanced fibrosis. The mechanism of back pressure in this case probably arises from the fact that the bladder's function as a reservoir is interfered with.

Dr. Baehr. The puzzling clinical picture is now explainable as the end result of a long standing chronic gonorrheal infection of the posterior urethra, with involvement of the bladder and replacement of the bladder muscle with fibrous tissue. Thus, the bladder was converted into a fixed, inelastic sac, which in turn led to back pressure and the hydronephrosis.

Reported by *M. Ellenberg, M.D.*

CLINICAL NEUROPATHOLOGICAL CONFERENCE

JOSEPH H. GLOBUS, M. D., *presiding*

Monday, February 10, 1941

*Case 8.** Metastatic Carcinoma of the Brain

[*From the Neurosurgical Service of Dr. Ira Cohen*]

History: (Adm. 447872; P.M. 11335). V. L., a 55 year old man, was admitted to the Hospital on October 26, 1939. The past history revealed that the patient had been in a sanatorium on four occasions before 1935 for what was reported to be "manic-depressive psychosis." He had been deaf for ten years. The patient dated his present illness six weeks prior to admission to this Hospital, when he began to suffer from headaches, although for the entire previous year "eye strain" and headaches followed attendance at the movies. On October 9, seventeen days before entering the Hospital, he became nauseated and vomited. This persisted for ten days. He also had some dizziness which caused him to stagger. He would become drowsy, but could be aroused. His family noted lack of attentiveness, some memory defect, difficulty in recognizing people and, at times, incoherent speech. The patient complained of pain behind the right ear.

Examination: The pupils were normal. The fundi showed slight indistinct disc margins. There was corneal hypesthesia and a mimetic facial weakness of the right side. The abdominal reflexes on the right side were diminished. There was an inconstant bilateral Babinski sign. Sensation was normal. When his arms were held outstretched with the eyes closed, his right arm tended to drift outward. On the right side adiadochokinesia and some dysmetria in the finger-to-nose test were present. When his head was flexed forward there was pain in the right occipital region with some resistance to further flexion. When seated, he tilted his head toward the right shoulder. He was drowsy and, if left alone, tended to fall asleep. When aroused, his attention could only be held for a few moments. He was disoriented with regard to time and place. He frequently erred in naming objects and exhibited perseveration. When asked to read, he would read only a few words and then commence again at the beginning. Spontaneous speech appeared to be correct, but was not sustained.

Laboratory data: Urine and blood tests were normal. The Kahn reaction was negative. X-ray examination of the chest on October 27 was reported as negative and this was confirmed on November 16. A ventriculography performed on October 28 showed bilateral symmetrical dilatation of both lateral ventricles and of the third ventricle; the iter and the fourth ventricle were not visualized. The cerebrospinal fluid was not examined at the time of admission.

Course: A diagnosis of brain tumor was made, although its location was not determined. The mental picture was classed as an acute confusional state with an organic background. On November 2 his neck was found to be rigid and a bilateral Kernig sign was present. The mimetic facial weakness on the right was still present. He was completely disoriented. He began to cough up small amounts of blood-streaked sputum and, despite the normal

* The first seven cases were reported in previous issues of the Journal (Vol. VIII, Nos. 3, 4, 6; Vol. IX, Nos. 1 and 2).

x-ray appearance of the chest, it was felt that he had a bronchial carcinoma with diffuse metastatic infiltration of the meninges. A neurosurgeon, who was called in consultation, felt that there was a tumor in the left cerebral hemisphere. In the interim the patient had become very drowsy. A lumbar puncture yielded cerebrospinal fluid under a pressure of 130 mm. of water. The patient declined rapidly and died on November 18, 1939, three weeks after admission.

Necropsy findings: Brain, gross: The convolutions of the brain were slightly flattened and there was bulging of the floor of the third ventricle. The right lobe of the cerebellum was larger and softer than the left and the convolutions were flattened. On sectioning of the brain, both lateral ventricles and the third ventricle were symmetrically enlarged (fig. 22). The fourth ventricle was also enlarged and deformed. In the cerebellum there

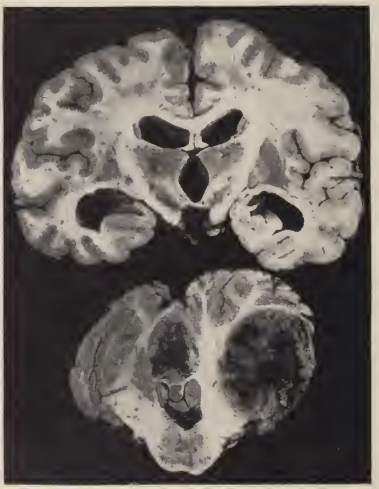


FIG. 22 (Case 8). Coronal section of the brain showing symmetrical internal hydrocephalus and the two metastatic tumors in the cerebellum.

were two tumor deposits (fig. 22). One, measuring 4 cm. in diameter, was situated in the ventral two-thirds of the right lobe. It replaced the cerebellar folia and reached the surface of the cerebellum. It also occupied part of the white matter and the right dentate nucleus. A second tumor mass, measuring $2\frac{1}{2}$ cm. in diameter was situated in the vermis practically completely replacing it and leaving only the tonsillae and uvula. Both neoplastic growths presented a granular appearance, grayish-pink in color, alternating with darker areas. Several areas of frankly necrotic tissue were present.

The general necropsy revealed a carcinoma of the right main bronchus with extension to the left main bronchus and with regional metastatic nodules.

Microscopic: Sections of the tumor in the cerebellum revealed a very cellular tissue broken up into an irregular mosaic by cores of connective tissue. The tumor nuclei contained a moderate amount of chromatin and varied in size and were either oval or round in

shape. There was very little cytoplasm around the nuclei. Connective tissue was very abundant in places and contained many blood vessels with hypertrophied walls. Extravasated blood and serum were also seen. In one part of the tumor necrosis was present. The cerebellar tissue adjacent to the tumor showed infiltration by neoplastic cells, areas of disorganization, and congested blood vessels. A section of cerebral cortex distant from the tumor, apart from congestion, showed no pathologic alterations.

Comment: Dr. Globus: Of significance in this case is the disclosure of neoplastic emboli in some of the blood vessels in the proximity of the tumors.

Reported by *T. Meltzer, M.D.*

*The Story of the Mount Sinai Hospital, of which the first four installments appeared in preceding numbers of the Journal, is offered in celebration of the Hospital's ninetieth birthday. In its present form it consists mainly of brief historical notations which to some extent reflect the "way" of medicine in New York and elsewhere, as well as the changing environment since 1852. It has been compiled by Miss Jane Benedict from Hospital records, correspondence, medical and historical literature, and interviews with those who have been both eye-witnesses of and contributors to the Hospital's progress. It is presented mainly as source material from which later a more complete history of the Hospital is to be written.**

The preceding installments were devoted to a description of the founding and the founders of the Jews' Hospital in New York, the organization of its first Medical Staff, and the early years of its activity, with a brief account of contemporary medical and surgical practices, medical education, and nursing. Some of the physicians and surgeons influential in shaping the Hospital's tradition were depicted and a brief account of the services rendered by the Hospital during the Civil War was given.

This installment is concerned with important phases in the Hospital's history: changing its name, outgrowing the old home, and preparations for a larger one. The role of the hospital in the cholera epidemic and the Boyne Day riots are related as well as the accident which finally determined the decision to move into new quarters.

THE FORMATIVE YEARS, 1852–1872

V

While medical progress in this country was being hampered by the events of the Civil War, it was making rapid strides abroad. Uppermost in the minds of the investigators was the cause of infection. Louis Pasteur, in the vanguard of the experimentors, opened a new and most important chapter in medicine by his discoveries, which brought to an end the days when cleanliness of hands and instruments was not considered essential to the success of an operation and when festering of a wound was spoken of as "laudable pus."

Lister, having become aware of the discoveries of Pasteur, and realizing the importance of microorganisms in his surgical failures, turned to chemical antiseptics as a means for the prevention of infection and chose carbolic acid for that purpose. He published the satisfactory results of this method in a paper, *Antiseptic Principles in the Practice of Surgery.* This was the background, in 1863, when the problem concerning patients infected with typhoid fever, which had troubled the Board since the year the Hospital first had received patients, was finally settled. In a resolution from the Medical Board, signed by Drs. Jacobi, Schilling, and Henriques, the difference in contagiousness between typhus and typhoid fever was set forth:

* Corrections, if errors of fact or interpretation are discovered, and additional information which may help to make the picture more complete, are welcome and may be addressed to the Historian of the Hospital.

"Whereas typhoid fever is, under ordinary circumstances, no contagious disease, the cause of its becoming so being rare both in this City and Hospital, there can be no objection to admitting cases of typhoid fever into the Hospital. The Medical Board would recommend such cases to be intermixed with other patients in the same wards, unless there may occur apparent reasons for isolation in a separate ward.

"Whereas, further, typhus fever although more contagious than the former, will not develop its contagious character in a clean and spacious Hospital in the same degree as in the filthy and overcrowded abodes of poverty and disease, and, therefore, will not produce the same danger for any member of the community at large.

"Whereas, then, by running a very small risk from the contagiousness of the fever, will avert a very great danger from the community, the Medical Board recommends these cases to be isolated in an airy and spacious ward."

In 1865 New York found itself faced with a serious problem which demanded a solution—the need for a quarantine station. Previous to 1858 there had been such a building on Staten Island, but the citizens there objected to its presence because they felt it unhealthy and considered it detrimental to the value of real estate. When the city refused to do anything about its removal, the incensed citizens burned it down. After that there was no place for isolating immigrants with contagious diseases[74] and New York paid bitterly for this neglect. In November of 1865, the ship Atlanta sailed into the harbor carrying immigrants with the dreaded Asiatic cholera. New York still remembered how heavily it and other cities had suffered from the cholera epidemic of 1832. In an effort to prevent repetition of the three thousand deaths which had resulted from the earlier epidemic[58], the Atlanta passengers were transferred to an old hulk lying in the harbor. A Board of Health was appointed, with Willard Parker, Consulting Surgeon to the Jews' Hospital, as one of the four commissioners[74]. The minutes of the Hospital Directors' meeting of December 17 of that year record a resolution to throw open the Fourth Ward to cholera victims.

By 1866 there was still no quarantine station, and another ship with cholera victims among its passengers entered the harbor. An epidemic broke out in the city. There were 1205 deaths. By June 3 of that year the Directors of the Hospital rescinded the resolution of the previous year because they found that the Board of Health was caring for such patients. They determined, however, to be in readiness to accept such cholera victims as might apply. Dr. Teller's report for the year 1866 notes that, "... the Hospital was kept entirely clear of cholera Asiatica, by giving proper attention to the first symptoms of cholorine and diarrhea, and by using proper disinfectants."

Ever since it first cared for wounded soldiers in 1862 the Hospital had maintained its completely non-sectarian policy. In 1864, the Executive Committee had reported, "The Committee deem it proper to observe that many of those admitted to the Hospital were not of our faith, no distinction ever being made as

[74] Wilson, James Grant: Memorial History of the City of New York, Vol. 55, New York History Company, 1893.

to either the nationality or the religious belief of the sufferer." Valentine's Manual for 1865, in describing the Hospital, states, "Although the Hospital was founded by gentlemen of the Hebrew faith, yet the benefit of this excellently managed institution, which is supported entirely by the contributions of its members, is freely extended to all, of every religion or nationality, and the visitor will often find under the care of its officers, sufferers who widely differ in the matter of religious beliefs." Yet it was difficult to convince the public of this non-sectarian policy, and the Hospital was suffering accordingly.

The 1867 report explains this: "The Directors have had to encounter much opposition in making their claims on the charitable fund of the city and state in consequence of the name of the Hospital, it being alleged as 'sectarian' and not for the benefit of all who may seek its protection and care."

Because of this difficulty, by special act of the Legislature in 1866, the Jews' Hospital in New York became "The Mount Sinai Hospital." The name was chosen from the words spoken to Moses on the way to Mount Sinai: "I, the Lord, am thy healer."[75]

The close of the Civil War initiated a period of expansion in New York. Above Forty-second Street the city was sparsely settled. There were 25,261 vacant lots below Eighty-sixth Street.[74] But the years after 1865 saw the trend of the city northward. Speculation and a building boom, encouraged by the Tweed Ring which had ridden to power, reached their heights in 1871, then waned until they sank into the panic of 1873. During these years Madison Avenue was graded. St. Nicholas Avenue was created. Seventh Avenue and Broadway from Twenty-fourth Street to Central Park were broadened. The city began to assume something of today's aspect. In 1865 a paid Fire Department replaced the volunteer group which had previously served the city, and hand-pumped engines were replaced by steam. That same year saw the introduction of "French Flats," the predecessor of the modern apartment house. Seasoned New Yorkers predicted the failure of so crazy a scheme, outraged at the notion of asking any but slum dwellers to house their families in a series of rooms all on one floor. Nevertheless, the idea "took", and apartment dwelling became a reality.

Transportation was also a problem that had to be solved. In a growing and industrialized city whose northern limits were constantly pushing uptown, there was still no convenient way of travelling from one end to the other. The urgency of the traffic problem is apparent in the following description of a Frenchman who visited New York in 1868.

"Broadway, the principal thoroughfare, is often beset with dreadful dangers—wagons, drays, and carriages of every description choking it up for blocks, as well as many by-streets and avenues. Foot passengers have often to wait very long before they can cross from street to street—unless they belong to the fair sex, in which case they are soon escorted over, as polite policemen seem to make it their principal business to open a way for the ladies."[76]

[75] Interview with Capt. N. Taylor Phillips, son of Isaac Phillips, June 15, 1938.

[76] Longchamp, Frederick: Asmodeus in New York, 1868.

In 1866 an elevated railroad, operated by a cable and running on a single track had been created. It ran from Battery Place through Greenwich Street to Ninth Avenue and Thirtieth Street, terminating only a few blocks from the Hospital. Steam was later substituted for the cable, but presently the line failed.[74] Between 1868 and 1870, two underground roads as passageways for traffic were chartered, but never constructed. Not until 1878 was a steam elevated line to be built, from Rector Street to Central Park.

The means of getting from New Jersey, Brooklyn, Staten Island and Williamsburg to New York assumed great importance in the winter of 1866–7. Ferries usually carried the farmers who brought their produce to the city from the outlying districts, but during that winter the rivers around Manhatten Island were frozen much of the time. It was then that New York turned its mind to the construction of bridges. In 1867 John A. Roebling was chosen Chief Engineer of the New York Bridge Company. The erection of the Brooklyn Bridge was begun, although it was not completed for many years.[74]

This period during which New York was beginning to meet the problems of a growing cosmopolitan city had its effect on the little Hospital on Twenty-eighth Street. The surroundings, which had been so rural when Sampson Simson donated the first lot of ground, where for many years tomatoes could be picked and goats were free to wander in the open spaces, had changed slowly. As elevated lines were built, as new streets were opened and old ones graded, as the city pushed its way uptown, the Twenty-eighth Street neighborhood took on an industrial aspect and the old residences degenerated into slums. The Hospital's surroundings were no longer either quiet or healthy.[69] A contemporary account says:

"At the time of the opening of the Hospital, the neighborhood was clean, airy and quiet. But during the last few years the building has been surrounded by factories, breweries, and workshops, whose steam-engines are puffing day and night, to the great annoyance of the patients, who sigh for quiet and rest."[77]

Moreover, the Hospital buildings which accommodated only sixty-five patients even with the additions made from time to time, were becoming increasingly inadequate. The report for 1867 shows that there were 594 applications for admission in the previous year, and 564 were accepted. The value of Mount Sinai to the district it served is amply indicated by comparison of that year's admissions with the numbers admitted in the first six years of the Hospital's existence: 1855, 113; 1856, 212; 1857, 220; 1858, 250; 1859, 221; 1860, 269.

These early efforts to give adequate service to the community have been amply borne out in the modern Mount Sinai's work. In 1941 the Hospital cared for 17,222 in-patients and 27,654 out-patients, a total of 44,876 individuals.

On December 28, 1866, the Medical Staff addressed to the Board of Directors a letter condemning the First Ward during the summer months because " . . . its proximity to the street renders it obnoxious from the effluvia arising from the garbage and its surroundings. The very insufficient ventilation is injurious to the patients and detrimental to the health of the nurses and attendants." More-

[77] Richmond, John Fletcher: New York and Its Institutions, 1871.

over, the report of the House Physician and Surgeon pointed out that the Fourth Ward was unusable in winter because the heat from the furnace was not adequate to reach more than three wards. In 1855 the Hospital had had the best that was known in ventilation, heating, and sanitation; but in 1867 engineering had made sufficient progress to leave the methods of 1855 behind. For these reasons the 1867 report states:

"The location of the Hospital, we regret to say, becomes daily more and more unpleasant, and its size and accommodations inadequate for the wants of our people. . . . The chief essential, in the locality of a Hospital, is pure air and plenty of it, whilst its surroundings should be cleanly and cheerful, calm and tranquil, in all of which health-promoting requisites, it is to be regretted, the present site is quite deficient."

The incident which finally convinced the Directors that the Hospital must be moved occurred in 1868, when a steam boiler exploded in an adjacent factory.

"The scene of this frightful accident was about one hundred feet from the Hospital. . . . It is sufficient to say that the buildings were in danger; the walls were shaken, the windows scattered; but we are glad to add no serious damage was done to the Institution. The panic among the patients having been allayed, and their terror tranquilized, the doors of the Hospital were immediately opened to the wounded, the dying and the dead."[78]

On November 2, 1867, the Finance Committee was authorized to buy ten lots of land running from Sixty-fifth to Sixty-sixth Street west of Fourth Avenue. On October 6, 1868, however, a grant was secured from the city for twelve lots running from Sixty-sixth to Sixty-seventh Street on Lexington Avenue on a ninety-nine year lease at the nominal rate of one dollar per year. This was accomplished through the efforts of Emanuel B. Hart, who had been a member of Congress and Surveyor of the Port of New York and who was the Hospital's Vice-President. The lots which the Finance Committee had bought were re-sold, and Mount Sinai made preparations to erect a new building which would answer its needs more adequately.

In planning for this first major expansion, the Trustees were able to count on the cooperation of a new organization which proved consistently helpful to the growth and functioning of the Hospital. The Ladies' Auxiliary Society was organized in 1868 ". . . to assist The Mount Sinai Hospital in the furnishing of such articles of clothing and other wares for the inmates of the hospital as the Board of Directresses may determine and in general to perform such other acts as may tend to the well-being of said hospital."[79]

While membership was open to "any lady . . . on the payment of one year's dues," many of the most energetic members were the wives or relatives of men active in the affairs of the Hospital. Mrs. Benjamin Nathan, the first treasurer of the Society, was the wife of the President of the Hospital Board, who at the first meeting "eloquently addressed the Ladies on the subject of Charity, and

[78] Annual Report of the Directors of The Mount Sinai Hospital, 1868.
[79] Article I, section 2, By-Laws of the Ladies' Auxiliary Society, 1868.

the beneficial and humane objects of the Hospital and its Auxiliary Society."[80] The first President was Mrs. Henry Leo.

For many years the Ladies' Auxiliary Society was the chief helpmate of the Hospital, furnishing all the linens and beddings used in the wards, providing flowers, decorations, and hostesses at social functions, assisting in fairs and bazaars. On one occasion the three stands sponsored by the Society at a Fair netted $11,201.52.[81]

An incredible amount of cutting and sewing was accomplished at the weekly meetings. As the needs of the hospital grew, however, it became necessary to employ outside help, "thereby assisting many poor women who take this way of supporting themselves."[82] The economic burden kept pace with the hospital's growth, until by 1909 the Society was expending approximately eight thousand dollars a year, "all of which they have provided by their own efforts."[83] The thousands of dozens of towels, the sheets and pillow cases, blankets and garments contributed by the Society in later years represented an increase far beyond the expectations of the ladies who elected their first Officers and Board of Directresses in the committee room of the Synagogue Bnai Jeshurun on March 15, 1868.

In the year 1871, the last year Mount Sinai remained in the Twenty-eighth Street building, a public misfortune occurred in which the Hospital again took part. In 1870 the Orangemen of New York had held a parade to commemorate the Battle of Boyne. The music they played, especially *Boyne Water*, angered the Irish and a battle ensued. The following year, when the Orangemen applied for a permit to parade on Boyne Day, the permit was refused by the Superintendent of Police on the ground that such a parade would again provoke a riot. This was apparently done with the sanction of Mayor A. Oakey Hall. Public opinion was aroused, and a meeting was called to protest the refusal. Governor Hoffman was called upon and the permit finally granted. Meanwhile, most of the Orange lodges, under the impression that they were not going to be allowed to parade, had left New York to celebrate out of the city limits. Therefore, when the permit was granted at the last moment, there were only about one hundred Orangemen ready to parade. Almost completely surrounded by police guard and regiments, the parade started. When it had proceeded as far as Eighth Avenue between Twenty-fourth and Twenty-fifth Streets, a shot was fired from one of the tenements. Some members of the Seventh Regiment lost their heads and without orders, fired into the holiday crowds that lined the sidewalks. A riot immediately ensued. Fifty-four people were killed and wounded. Mount Sinai and Bellevue Hospitals gathered up the dead and dying. The case book of the Hospital for 1871 records twenty-five victims "injured at the riot in Eighth Avenue."[74] The halls and corridors of the already overflowing Hospital were lined with those unfortunates who were cared for on hastily improvised beds.[67]

[80] Minutes of the Ladies' Auxiliary Society, March 15, 1868.
[81] Minutes of the Ladies' Auxiliary Society, December 30, 1875.
[82] Minutes of the Ladies' Auxiliary Society, December 18, 1893.
[83] Annual Report, page 30, 1909.

Those first formative years spent in the Twenty-eighth Street building saw the development of a Hospital which became increasingly vital to the Community it served. In 1870 there were 677 patients cared for in the Hospital, 1,064 out-door patients treated. Of these 1,741 men, women and children, only twenty-two contributed anything to their expense.[84] From an intimate group of benevolent men who had conceived the idea of aiding the sick poor of their own faith, the Hospital had widened to include a group of all nationalities and races, serving the public irrespective of religion. In a growing city which sorely needed such institutions, it had made for itself a recognized place as a hospital which would rise to meet emergencies when immediate medical care was required.

The next installment will be devoted to a description of the Hospital's new home on Lexington Avenue between Sixty-sixth and Sixty-seventh Street, and related circumstances and events.

[84] Annual Report of the Directors of The Mount Sinai Hospital, 1871.

ABSTRACTS

Authors' Abstracts of Papers Published Elsewhere by Members of The Mount Sinai Hospital Staff

Members of the hospital staff and the out-patient department of TheMount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Jaundice in Infants and in Children—The Icteric Index as a Method of Determining the Type of Jaundice. M. Reiner and S. B. Weiner. Am. J. Dis. Child. 61: 752, April 1941.

The relation of the icteric indexes determined by the water and acetone methods may be explained by a difference in the physical state of the bilirubin in cases of regurgitative and of hemolytic icterus. The determination of the icteric index of a specimen of jaundiced serum by both the water and the acetone method is proposed as a means of differentiating the hemolytic from the non-hemolytic type of jaundice.

In cases of pure hemolytic icterus the ratio of the icteric index obtained by the water method to the acetone method is 1:1. In specimens from patients with obstructive and hepatic jaundice, so-called "regurgitative icterus" the ratio of the water to the acetone method is 2.5-3.0 to 1.

Icterus neonatorum falls into the group of hemolytic icterus according to this test.

Myopia and Avitaminosis. J. Laval. Am. J. Ophthalmol. 24: 408, April 1941.

There is experimental proof that a deficiency of vitamin A will cause changes in the ocular tissues of experimental animals primarily in the cornea and sclera. There is insufficient proof to indicate that D avitaminosis *alone* will cause changes in the cornea and sclera. Infants and children in New York City get sufficient amounts of vitamins A and D; this is true of those children coming from poor as well as from the well to do homes. Excessive dosages of viosterol has caused unhappy results in children, and excessive dosage of viosterol in adults may be carcinogenic in effect. Myopic persons should not constantly wear their correction for myopia for distance vision unless vision without the glasses is so poor that the wearing of glasses is absolutely necessary. But the myopics must always wear their correction for close work.

Hepatic Duct Visualization Following Oral Cholecystography. B. Copleman and M. L. Sussman. Radiology, 36: 465, April 1941.

Four cases are reported in which after cholecystography and the ingestion of a suitable meal, the cystic, common and hepatic ducts were outlined. This finding is considered as possibly abnormal and presumably due to a disturbance in the reciprocal relationship of gall-bladder contraction and relaxation of the sphincter of Oddi.

The clinical symptoms in these cases are similar to those of biliary dyskinesia. However, without cholangiographic confirmation, this clinical diagnosis cannot be established and a definite correlation cannot be made. It is possible, however, that the roentgen-ray findings described should be considered as offering confirmatory evidence of the diagnosis of biliary dyskinesia.

Incidence of Neurosis in Cases of Bronchial Asthma. V. Schatia. Psychosomatic Med. 3: 2, April 1941.

In this study an attempt was made to determine whether the development of asthma as a reaction to an inner conflict was uniformly associated with any particular personality type. Rorschach records of forty patients suffering from bronchial asthma were obtained,

scored individually, then compared with each other and with two control groups of normal persons. After eliminating mental defectives and those with cerebral disease, only three of the entire group of patients remained who might be called clinically free from neurosis or neurotic character traits by psychiatric tests. Analysis of the Rorschach records confirms the impression based on psychoanalytic methods that asthmatics tend to have compulsive personalities without evidence of phobias or compulsions.

An Automatic Blood Pressure Recording Apparatus. H. Weiss. J. Lab. Clin. Med. 26: 1351, May 1941.

A portable apparatus is described which automatically records systolic and diastolic pressure, pulse pressure and pulse rate. The results are comparable to those obtained by the auscultatory method. Determination can be made over any desired period of time or at any intervals, with the subject asleep, at rest or while engaged in moderate activity. The author further indicates the availability of the instrument as part of a cardiodynamometer to measure relative cardiac efficiency. The principle of the machine is a fluctuating base line synchronized with the pressure changes in a blood pressure cuff, and on this is imposed the sounds recorded microphonically at the antecubital space. The instrument is illustrated in drawings.

Ileocolostomy with Exclusion in Treatment of Regional Ileitis. R. Colp and L. Ginzburg. New York State J. Med. 41: 982, May 1941.

The operation of ileocolostomy with exclusion was performed on 22 patients with regional ileitis. In 19 cases the results were favorable as regards the disease in the excluded loop. One of the unfavorable results was in a case of complicated ileosigmoidal fistula for which the operation is no longer recommended. The authors feel that proximal progression of the ileitis is not dependent upon the type of operation performed as it occurred in only 1 case in this series as compared to 3 cases in a series of 13 in which the diseased segment was resected. They feel that such proximal progression may be prevented by performing the exclusion and anastomosis well proximal to the last visible area of disease.

Solitary Eosinophilic Granuloma of Bone. M. H. Bass. Am. J. Dis. Child. 61: 1254, June 1941.

Two patients suffering from an unusual type of solitary eosinophilic granuloma of bone occurring in childhood are described. In one case the lesion was in the skull and in the other in a rib. Both were operated upon and cured, one having been followed for seven years and the other for two years. This condition, of which eight other cases have been reported in the literature, is apparently a distinct disease entity. Roentgenologically it fulfills all the criteria of malignant disease of bone. Clinically as well as roentgenologically this benign lesion resembles malignant disease; the patient may be permanently cured by operation and irradiation.

A Critical Evaluation of the Results of Routine Conservative Treatment of Syphilis. H. T. Hyman. Bull. New York Acad. Med., 17: 467, June 1941.

It is estimated that there are approximately 6,000,000 people in the United States whose blood serology gives a positive complement fixation reaction for syphilis. In the present national emergency it is of prime importance to establish a national policy for the treatment of this dread disease which has far reaching consequences physically and economically to the individual and to the State.

The difficulties of evaluating clinical results are summarized. They relate to the immunity mechanisms in the host; the dose and virulence of the parasite, and, most particularly, to the host-parasite interrelationship. The latter is the factor of greatest importance, since carefully conducted studies suggest that as many as two-thirds of all infected individuals live and die without clinical manifestations of the disease.

The evaluation of specific therapy must be reckoned in terms of the spontaneous course. These calculations are made increasingly difficult by the fact that specific therapy is con-

ducted according to a variety of schemata. The common factors in routine conservative chemotheraphy of syphilis are the repeated use, over long periods of time, of small doses of the specific heavy metals. The great problem in this type of therapy is that of "case holding" and "case loss." Nation-wide figures indicate that "case loss" approximates 95 per cent under all conditions and exceeds 80 per cent under the optimal conditions established by the Cooperative Clinical Group working under the auspices of the United States Public Health Service.

The published figures of the syphilologists ignore "case loss." Consecutive series have never been reported. Thus, the efficacy of routine conservative treatment has been adjudicated by data obtained from the records of the minority of patients who faithfully continued treatment, ignoring the majority who lapsed. It is obvious from this fact alone that routine conservative treatment cannot satisfy the requirements of our national approach to this serious problem. However, if the best published figures of the most competent syphilologists are analysed in the light of their short-comings, it becomes apparent that only in those patients with early syphilis, who receive continuous and continued treatment (2.5 per cent of all who initiate therapy) do the percentages of cure clearly exceed the expectancy from spontaneous course.

This statement does not apply to syphilis of the nervous system but refers to all other manifestations of syphilis, including early latency, late latency and the various types of visceral lues.

Two Unusual Cases of Chorioepithelioma. I. C. Rubin. Am. J. Obst. & Gynec. 41: 1063, June 1941.

Two contrasting cases of chorioepithelioma were described: one was a young woman of twenty-three whose only pregnancy was terminated by induced abortion which was followed by hydatid mole and very small myometrial chorioepithelioma. The latter escaped the pathologist's observation until after many sections of the uterine wall had been made. The persistence of a positive Friedman test in the absence of evidence of pulmonary metastasis gave the clue to the diagnosis. Incidentally, the patient developed a carcinoma simplex of the left breast two years later.

The second case was that of a woman forty-four years of age who had had seventeen pregnancies resulting in thirteen children and four miscarriages. The last pregnancy occurred one year ago and terminated in a miscarriage. Without premonitory symptoms profuse uterine hemorrhages appeared and compelled the patient to apply for treatment. The lesion apparently originated within the cervix or the isthmus of the uterus at the level of the internal os and resembled a placental mole in the process of extrusion.

A Case of Hand-Schüller-Christian Disease. A Case in Which Lymphadenopathy Was a Predominant Feature. M. Freund and M. L. Ripps. Am. J. Dis. Child. 61: 759, April 1941.

A case of Hand-Schuller-Christian disease is presented first, because it gives substantial evidence in support of Lederer's observation that the lesion is initially inflammatory and that the lipoid deposition is a secondary development; second, because of appearance of the predominant symptoms at the early age of 7 weeks, in the form of enlarging lymphadenopathy of the inguinal and cervical nodes. Two biopsies performed on lymph nodes between 7 and 9 months showed proliferation of reticulum cells and giant cells, intermingled with plasma, lymphocytic and polymorphonuclear cells, but no cholesterol infiltration. The typical osseous changes did not appear until 13 months. At autopsy, age 2 years, lipoid granulomas typical of Hand-Schüller-Christian disease were found in paravertebral fascia and both lungs, while the lymph nodes exhibited only those changes observed at biopsy.

EDWARD GAMALIEL JANEWAY LECTURE

NEWER CONCEPTS OF INFECTION AND IMMUNITY AND CHEMISTRY'S PART IN THEIR DEVELOPMENT, I[1]

MICHAEL HEIDELBERGER, PH.D.

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First of all I want to thank the chairman for his very kind introduction. Some years ago I had the privilege of introducing Welch and Janeway lecturers to audiences in this hall and I wish to express my appreciation of now seeing this process reversed, as chemists say, and being myself introduced as a Janeway lecturer. In the provisions of the gift of the Janeway lectures it is emphasized that experiments in the laboratory branches of medical science be given precedence and it is especially in the field of immunology that chemistry plays a decisive part, and has contributed to many of the more modern concepts. So, even though my subject is a restricted one, I feel that it comes within the scope of this Lectureship.

The chemist, looking from his admittedly narrow horizon, considers immunity to infectious disease as an interplay of antigens and antibodies, resulting perhaps in the disposal of the invading microorganism or virus. Let us consider first newer investigations which have led to a somewhat different view of the concept of antigens. A great many of you doubtless have seen in the literature a statement such as, "horse serum was used as antigen," and this was often repeated since horse serum was one of the most available sources of foreign protein.

Now let us look at horse serum through modern eyes, the eye in this instance being the Tiselius electrophoresis apparatus, which with its improved optical and recording devices, shows a peak for each protein component moving in the electric current with a different velocity. As you see, there are at least four peaks due to separate components: albumin and α-, β-, and γ-globulins.

Most of the natural sources of antigens are now known not to yield single proteins but mixtures. A good many of the earlier immuniological observations were difficult to interpret because this was not understood at that time.

Now what else can we say about antigens? You will gather from what I have said that certainly many proteins are antigens and it may also be said that a very large number of antigens are proteins. What are some of the factors which make an antigen and confer upon it the specificity which characterizes it as a definite antigen? We owe a great deal of our knowledge to Landsteiner's studies. These emphasized the importance of the amino groups and, in extension of the work of Obermayer and Pick, showed that if a substituent were introduced into the phenolic radical of proteins (tyrosine groups) the specificity

[1] Transcript of Lecture delivered in The Blumenthal Auditorium of The Mount Sinai Hospital, April 7, 1942.

changed in a way characteristic for the substituting group. It was possible to show that the new specificity was very sensitive to the nature of the radicals introduced into the protein.

Denaturation also causes a change of specificity, and in our laboratory we have shown that if one substitutes hydroxyl groups with phosphoryl groups there is also a change of specificity, so that almost any appreciable alteration will result in a definite change in immunological specificity.

As you know proteins are made up of long chains or fabrics of some twenty amino acids. Their immunologic behavior and their chemical and physical properties vary so greatly that it is quite evident that proteins do not occur simply in the form of a single long thread or chain of polypeptides and amino acids. In general these chains or fabrics are rolled up or coiled up into more or less recognizable shapes. Very few proteins are truly spherical. Almost all form ellipsoids or polygonal structures. The molecules may be cigar-shaped, or flattened like pancakes. Tobacco mosaic protein seems to have the shape of a long rod. The bacteriophage of *B. coli* has a bizarre shape, with a head and tail. If it is really a protein, it certainly has a very definite shape and structure, not yet found in any other type of substance. In the last two instances these structures have been observed with the electron microscope.

Now most of you will remember that some time ago, in Avery's laboratory we found that type specificity among the encapsulated bacteria depended upon another kind of antigen. This type specificity was not protein specificity but due entirely to a peculiar group of polysaccharides resistant to the usual sugar-splitting enzymes. The specific polysaccharide of each pneumococcus type, for example, was distinctly different from those of the other types, and could be characterized by its distinctive physical and chemical properties. The sugars from types II and III pneumococcus were obtained free from nitrogen, and were the first instances in which immune specificity had been rigorously demonstrated in a class of substances other than proteins.

Now after this discussion of specificity what can be said about the requisite conditions for antigenicity? It is obvious that we must have a complex structure and large molecules and one of the important things seems to be the repetition of structural units. We have seen that this is a highly probable consequence of the modern views of protein structure we have just considered. We also know that the specific carbohydrate of type III pneumococcus, for instance, is made up of many cellobiuronic acid units. Some multiple of this unit must function as the immunologically reactive grouping, for when the carbohydrate is partially broken down by mild hydrolysis the fragments of two or more units are still reactive in anti-pneumococcus type III horse serum. Therefore, we assume that in order to function fully as an antigen a substance of large molecular size must be of such nature as to allow repetition of certain structural units. Possibly for this reason ordinary lipids do not appear to have a clear-cut antigenic function.

I think Dr. Landsteiner would add that any simple chemical substance may also function as an antigen especially if the chemical properties are such as to

allow its combination with protein to form new antigens. Complex structure is not necessary, therefore, if a number of molecules of a smaller entity can combine to form part of a larger structure.

There have, of course, been a great many theories as to what antibodies are and a great many theories on the origin of antibodies, but these theories could not be taken too seriously as long as there was doubt as to the true nature of antibodies. Only a few years ago immunologists were warned that antibodies might be merely ideas, rather than substances. Happily this attitude has changed and antibodies are now generally admitted to be modified serum proteins. Of course it was recognized years ago that antibodies usually occurred with the globulin fractions of serum or plasma and that they were very closely bound to these globulins. A few people were brave enough to say that antibodies were actually modified serum globulins, but many observers reported protein-free antibody solutions. Now I think we can trace this persistent error to a failure to recognize that many of the immunological tests for antibody function are much more delicate than the chemical reactions available for the detection of protein. All chemical tests for protein fade out at dilutions of 1 to 5,000 or 1 to 10,000 but one may still show that agglutinins for typhoid bacilli occur at dilutions of the order of 1 to 100,000. Of course, if the solution originally contained protein and no protein showed after dilution it was not lost in the process, but was just not detected.

With the use of new quantitative chemical microanalytic methods it was found possible to measure antibodies in sera in actual weight units. One could, for the first time, express antibodies in terms of specific nitrogen per cubic centimeter of serum, because after precipitation with a slight excess of antigen non-specific material could be washed out. Since the amount of nitrogen in the added antigen is known this may be subtracted and the residual nitrogen in the washed precipitate is due to the antibodies. Highly purified antibody solutions obtained as a consequence of information gained by these new methods were taken to Sweden and examined in the ultracentrifuge and electrophoresis apparatus. These antibodies proved to be typical serum proteins.

If any of you still doubt that antibodies are modified serum proteins I would be very glad to argue this point at the end of the lecture, but right now I hope that you are prepared to agree with me and we will go on with the consequences. Buchner's hypothesis that antibody contained fragments of antigen was proposed at a time when the actual nature of antibodies was not understood. This hypothesis never appealed to the chemist because chemists know that in a number of instances like repels like, rather than attracts. In 1932 Breinl, who was a pathologist, and Haurowitz, a chemist, proposed a theory that antibodies are formed by a modification of the normal process of serum globulin synthesis as a result of penetration of antigen or specific portions of the antigen to the site of globulin synthesis. The disturbance so brought about influences the character of that synthesis in a sense characteristic of the antigen so that when the modified globulin appears in the circulation and again encounters the antigen interaction is possible.

This not very clear picture was later expressed in a somewhat more definite form by Mudd. An extension of this hypothesis has recently been made by Pauling which is even more graphic and reasonable but as devoid of experimental basis as the Breinl and Haurowitz theory. So we are still awaiting substantiation of these theories by actual experiment. The Pauling hypothesis carried a second idea—that if one could take normal globulin, denature it, and fold it up again in the presence of antigen, artificial production of antibodies might be accomplished. Pauling now believes he has been successful in this, but we still have to wait for details of his experiments.

These theories of antibody formation have been given a physiological basis in recent years by Dr. Florence Sabin as a result of experimental work with a red protein dye. Dr. Sabin has observed macrophages in the omentum and cells of the reticulo-endothelial system and found that, at a certain stage of development, surface layers which form folds waving back and forth finally disappeared as if they were being extruded from these cells. She believed this to be the source of serum globulins and that the presence of an antigen (for example, the red protein dye) results in the specific modification of these globulins into the appropriate antibody.

A good many of you have scowled at me this evening as if to say "this is all very well, it contributes to our knowledge, but how does it touch upon my practice and what does it do for me?" These are important considerations, but I have purposely avoided mentioning the more practical aspects of these problems in the hope of seeing you at my next lecture on Friday night, when we will take up some practical applications.

EDWARD GAMALIEL JANEWAY LECTURE

NEWER CONCEPTS OF INFECTION AND IMMUNITY AND CHEMISTRY'S PART IN THEIR DEVELOPMENT, II[1]

MICHAEL HEIDELBERGER, PH.D.

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In the first lecture I reviewed the concept of *antigen* and tried to show that methods of modern scientific investigation, especially those of organic, physical and analytical chemistry, have led to quite radical changes and broadened our ideas on the subject. Also, since one effect of the action of antigens on the animal body is to elicit the formation of substances known as *antibodies*, the same methods have been useful in furnishing a clearer idea of what these substances are and in permitting their actual isolation and study in a state of analytical purity. There are two properties of antigens which render their behavior easier to understand both *in vitro* and in the animal body. Many antigens are proteins and in proteins one has long chains or fabrics of amino acids containing various radicals, some with polar groups such as —COOH or —NH_2 in excess, others with aromatic groups; proteins are made up of chains of these amino acids which roll or coil into various shapes and present surfaces with various structural fabrics. There is also a certain periodicity and possibility of the reappearance of these groupings; as a result proteins may be said to be of a multivalent character. If protein molecules happen to be antibodies produced by the disturbance caused by antigens in the animal body, then antibody in its reaction with antigen may, by virtue of this same multivalence, have available on its reactive surfaces more than one chemically active or immunologically reactive group. If the antigen is a polysaccharide, the evidence for periodicity and for the multivalence of immunologically (or chemically) reactive groups is actually complete because in the case of the pneumococcus type III polysaccharide we know that the actual structural unit is cellobiuronic acid and that the immunologically reactive grouping in the molecule is a small multiple of this. Cellobiuronic acid does not precipitate antipneumococcus type III horse serum, but partial degradation products of the type III polysaccharide containing two, three, and four of these units do give precipitates. In the undegraded molecule these multiple units are repeated several times, so that here we have a proven multivalent antigen.

Now let us consider multivalent antigen and antibody and their behavior in immunological reactions such as specific precipitation and specific bacterial agglutination. Such reactions become very much clearer because we can easily conceive of an initial antigen-antibody combination taking place, followed by further combination through other of these multivalent groupings with more

[1] Transcript of lecture delivered in the Blumenthal Auditorium of The Mount Sinai Hospital, April 10, 1942.

antigen and antibody molecules until huge aggregates are built up. These separate from solution if antigen and antibody were initially soluble, or if the antigen is a cell, clumping, or agglutination takes place. We have thus a very simple and satisfactory explanation for most of the phenomena of these immunological reactions.

I was going on to talk about practical matters, but I still have to say a word or two in regard to theory. Now, the precipitin reaction in rabbit antisera and the sera of many other animals is characterized by a curve of this kind: if one plots milligrams of nitrogen precipitated against milligrams of antigen added, the curve rises steeply from the origin and gradually falls off in slope. A small quantity of antigen nitrogen added gives a small amount of precipitate. The ratio of antibody to antigen in the precipitate decreases continuously over the greater part of the range of precipitation. This is characteristic of the precipitin reaction in rabbit antisera and some horse sera containing both anti-carbohydrate and anti-protein. Kendall and I have studied precipitin reactions of this type and have derived an equation making use of the law of mass action, describing these precipitin reactions quantitatively and simply. Pappenheimer and Robinson showed, in the toxin-antitoxin reaction, on the other hand, that the region in which the mutual multivalencies are best satisfied is the only region in which one gets precipitation and as a result one may make calculations which cannot be carried out in the precipitation reaction. Pappenheimer and Robinson thus showed that toxin-antitoxin flocculation takes place in the equivalence zone and with Williams and Lundgren they also calculated that the composition of floccules at the point of most rapid flocculation averaged TA_2. Now that is a very practical analytical control of which I think very little advantage has been taken. At this point a micro-analysis of the washed floccules for nitrogen is sufficient to establish, in actual milligrams per cubic centimeter, both the quantity of toxin and that of antitoxin in a toxin and an antitoxin of unknown potency, since they calculate that the unit of antitoxin contains about 0.0016 mg. of nitrogen and the molar composition of the floccules is TA_2. There we have one very definite practical step forward which I think will be made use of eventually—for it took many years after the actual demonstration before anti-pneumococcus sera were measured with any regularity in milligrams of antibody nitrogen instead of in vague relative units such as mouse protection, or agglutination titers.

A great many immunological reactions depend for their effect on a series of substances which are linked together under the name of complement or alexin. Examples are the lysis of certain bacteria and hemolysis or the lysis of red blood cells. Almost all reactions of bacterial disposal *in vivo*, as well as numerous *in vitro* reactions, many of great diagnostic value, depend upon the presence of complement. Until a short time ago it was generally considered that complement was a colloidal state and did not really exist as a chemical entity. Ehrlich, however, did not believe this; he believed complement was a chemical substance and that it actually combined with antibody in making lysis possible. Union

of red blood cell, antibody, and complement, all three, was essential for hemolysis of blood corpuscles. But Bordet's argument for the colloidal theory was preferred and accepted by most people.

In recent years two independent investigations have changed our knowledge of complement; one was the outgrowth of the newer quantitative analytical methods and the other was a study by Ecker and Pillemer in which they fractionated guinea pig serum in Cohn's laboratory at Harvard by fractional separation with salts and control in the Tiselius electrophoresis apparatus and the ultracentrifuge. They found it possible to separate two globulins, a first component, or "midpiece" and another product combining the properties of second and fourth components. They found that the third component was very difficult to separate and that it appeared in almost every fraction and there was some evidence of its being a lipid or lipoprotein.

Now, complement has usually been considered a great aid in immunological reactions and this is undoubtedly true in many instances. There is a great deal of evidence that phagocytosis is promoted by the presence of complement and certain groups of bacteria require the presence of complement before they can be lysed in the presence of immune antibodies. The precipitin reaction, however, takes place more rapidly if complement is not present or taken up. This typical immunological reaction does not require complement and the retardation caused by it is perhaps another point in favor of the picture I have shown of complement crowding into the framework of the antigen-antibody aggregate. We have had trouble in trying to investigate antibody in human sera and ran into difficulty with complement right away. It is not generally understood that human sera contain as much complement as guinea pig sera. In getting data on antibody in human sera it seemed desirable to get rid of human complement, which combines rather peculiarly and irregularly with human antibody of certain types. We do not know why the complement of some human sera does not combine with antibody and why complement of other human sera does combine. We have therefore taken it out and have found that we cannot do this in the usual way by heat inactivation, as small amounts of antibody are damaged in this process. One way of removing complement very simply is by addition of suitable amounts of an immune system such as rabbit anti-egg albumin and egg albumin, unrelated to that which it is desired to study. After removal of the precipitate (which contains the complement) antibodies may then be estimated in the supernatant. In this way determinations were made of the antibody content of the sera of patients who had recovered from pneumonia after treatment with sulfa drugs.

This brings me to the discussion of the quantity of antibody in antisera and it can be seen that human sera may actually show measurable quantities as the result of disease.

On occasion, when rabbits are given a long course of hyperimmunization their sera may show up to 7–8 or even 10 mg. of antibody nitrogen per cubic centimeter. Now if you stop to think, this means that in serum of this kind one-half

to three-quarters of the circulating globulin in the animal's serum is actually antibody protein. This would have been thought impossible until a few years ago.

Now there is one other point which I should like to mention and that is the relation of complement to "titers". Until recently we have had to be satisfied with complement titers and I think having to be satisfied with this has held back our knowledge. One other common source of trouble is illustrated by the comparison of the "titers" of anti-typhoid and anti-pneumococcus serum. I have seen statements in the most recent summary I know that typhoid antigen is a very much better antigen than pneumococcus antigen because of the very high titers of the sera produced (up to about 1:100,000), while anti-pneumococcus sera rarely exceed a titer of 1:1000. Now it takes very much less agglutinin to agglutinate a drop of typhoid bacilli than the same number of pneumococci. There may, therefore, be much more actual antibody in the anti-pneumococcus sera that agglutinate to a titer of 1:1000 than in anti-typhoid sera that agglutinate to a titer of 1:100,000. Actually one has to take an enormous number of typhoid bacilli before one adds an appreciable weight of antibody to them, while a vastly smaller number of pneumococci will add much antibody. This shows very clearly that one cannot compare titers in two different systems without consideration of the reacting proportions; the same applies to the comparison of the titers of the four components of complement. If Ecker and Pillemer's figures obtained by actual isolation are correct, there is more first component than fourth component in complement. However, the fourth component "titer" usually exceeds that of the first component and this can only mean that far less fourth component than first is required for hemolysis.

These, then, are a few of the more immediately practical considerations that have emerged from recent immunochemical studies. There are many others, and I hope some new ones may have occurred to you.

SERUM CALCIUM: CLINICAL AND BIOCHEMICAL CONSIDERATIONS[1]

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In determining the calcium content of the serum, one is accounting for all but a trace of the calcium in the blood. Most of this trace represents calcium lost to the serum in the process of clot formation; if the cellular elements of the blood contain any calcium, the amount is negligible (at most 0.1 to 0.2 mg. per 100 cc. of blood). For the purposes of this discussion, the concentration of calcium and other substances in the serum is being expressed in the conventional terms of mg. and gm. per 100 cc. of serum, unless otherwise indicated.

As determined in the morning after a fast of about 12 hours, practically all normal calcium values of human blood serum fall within the following limits: 9.5 to 10.5 mg. per 100 cc. for adults, 10.0 to 11.5 for children, and 10.5 to 12 for neonates and other infants. It should also be noted that these individual values remain practically the same from morning to morning. Indeed, through the balance maintained between the factors of calcium absorption, excretion, and storage in or release from the tissues, the serum calcium value of a normal subject readily restabilizes itself after any modification which food consumption, fasting, exercise, etc. may tend to introduce in the course of the day.

As we define the term, a definite *hypocalcemia* is represented by a value 1.0 mg. or more below the low normal limits just indicated—that is, by a value of: 8.5 mg. or less per 100 cc. of serum for adults, 9.0 for children, and 9.5 for infants. Correspondingly, a definite *hypercalcemia* is represented by a value 1 mg. or more above the high normal limits—that is, by a value of at least 11.5 mg. per 100 cc. for adults and 12.5 for children. These delimiting values for serum calcium can be stated in this rather dogmatic fashion because the current micromethods are accurate within 0.1 to 0.2 mg. per 100 cc., if a rigorously standardized technique is followed (Chart 1).

In cases showing border-line figures (that is, figures lying between definite hypocalcemic or definite hypercalcemic values and values just within the normal range at each end), the value obtained may present a problem of interpretation. For instance, in an otherwise normal adult, a value of 9.0 may reasonably be interpreted as normal for him, while in an adult presenting generalized osteoporosis such a value may justifiably be regarded as an indication of hypocalcemia. On the other hand, a value of 11.0 or 11.2 in still another adult might be associated with hyperparathyroidism.

One must pay attention not only to the amount of calcium in the serum, but also to the relation of the calcium to the inorganic phosphate and the proteins of the serum. In view of these correlations, it may be in place also to state here

[1] Delivered, March 13, 1942 as part of A Series of Lectures on Blood Chemistry marking the Ninetieth Anniversary Year of The Mount Sinai Hospital.

what we regard as the normal values for the serum inorganic phosphate and the serum protein. Practically all serum inorganic phosphate values normally fall between 2.5 and 4.0 mg. per 100 cc. in adults, 4.5 and 5.5 in children, and 5.5 and 6.5 in infants. Except perhaps in infants, values only 0.5 mg. below the normal lower limit in the various age groups may already indicate the presence of *hypophosphatemia*, and values 1.0 mg. or more above the normal upper limit may be stated to indicate a *hyperphosphatemia* (Chart 2).

As to the inorganic phosphate, we wish to note also the well known fact that the calcium and inorganic phosphate of the serum are reciprocally related in such a way that, on the whole, an increase in the phosphate is associated with a reduction in the calcium, and vice versa. This reciprocal relation is one to be

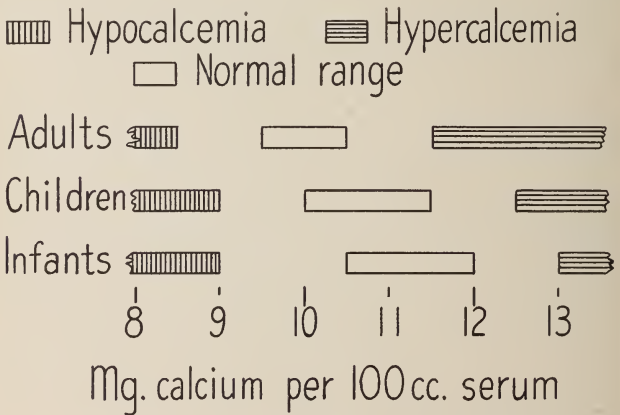

Chart 1. Ranges for normal and abnormal serum calcium values

expected theoretically, and it is observed clinically and experimentally under certain conditions. However, under other circumstances, it is masked.

In regard to the serum proteins, our experience is mainly with adults. Most of the values for total protein normally fall between 6.5 and 7.5 gm. per 100 cc. of serum, the albumin fraction being between 4 and 5 gm. and the globulin between 2 and 3 gm. We would interpret a total protein value definitely below 6 gm. as representing a *hypoproteinemia*, and a value definitely above 8 gm. as representing a *hyperproteinemia*. The protein values must be borne in mind in relation to the calcium values because, as is also well known, a considerable proportion of the serum calcium is combined with the proteins, most of this combination being with the albumin fraction. Thus a decrease in the serum protein, due to a decrease in the albumin fraction, is associated with a decrease of serum calcium, other factors remaining the same.

Significance attaches also to the forms in which the calcium is present in the blood, and much attention has been paid in particular to the questions of diffusibility, of the calcium-binding capacity of proteins, and of ionization. As a broad generalization, it may be stated that about 40 per cent of the serum calcium constitutes the non-diffusible calcium fraction and about 60 per cent the diffusible calcium fraction. The non-diffusible fraction consists of calcium proteinate except for a small amount of calcium bound to substances other than protein. The diffusible fraction consists very largely of positively charged ionized calcium, but this fraction does apparently also include (in certain animals, if not in man) a small amount of diffusible calcium compounds which are non-ionized.

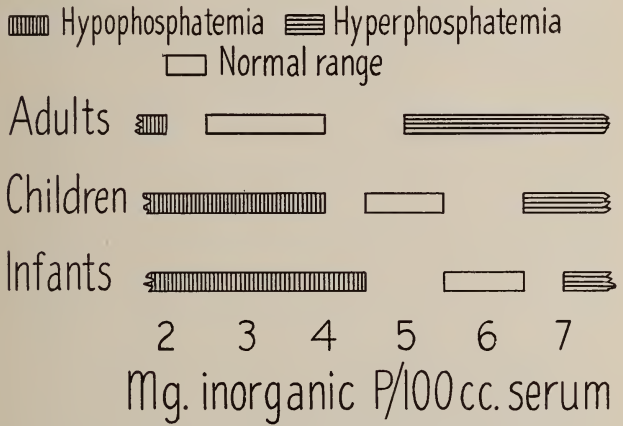

Chart 2. Ranges for normal and abnormal serum phosphorus values

The procedures for determining the diffusible fraction and the ionized calcium of the serum are not well adapted to general clinical use. However, the diffusible serum calcium fraction is sometimes estimated, in a given case, by determining the total calcium of the cerebrospinal fluid, since, in general, the two values are roughly equivalent, provided the protein content of the cerebrospinal fluid is not above the normal limit. Furthermore, as to the ionized calcium in the serum, one can calculate its approximate concentration by using the formula derived by McLean and Hastings or the nomogram based upon it. It should be noted, however, that McLean and Hastings (1) specifically point out that their formula and nomogram constitute an "oversimplification of the conditions which actually exist in the fluids of the body", and that, furthermore, they are not applicable to cases in which there is a calcium dyscrasia.

Starting with the observation of Salvesen and Linder that, in the nephrotic state, hypoproteinemia is associated with hypocalcemia, a number of investigators have tried to express mathematically the relation between the levels of calcium and protein in the serum. All these formulae account for: 1) a variable calcium fraction, which consists largely of calcium proteinate, and 2) a relatively constant calcium fraction, which consists largely of calcium ions (Chart 3). One of the formulae has also taken into account the inorganic phosphate value. Several equations, all derived empirically, have been proposed for ex-

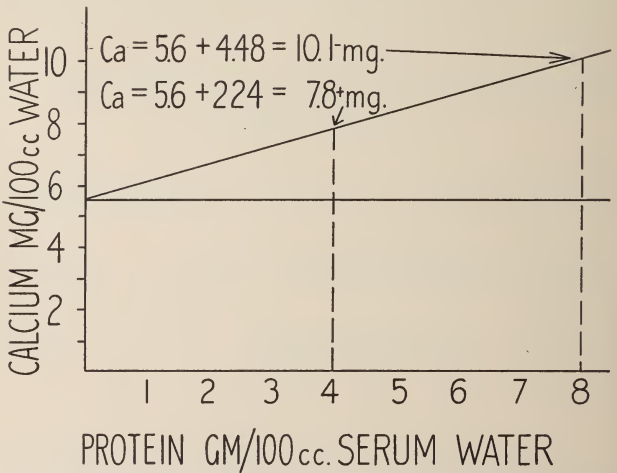

CHART 3. Adapted from Hastings, Murray, and Sendroy (2), to show proportionality between the "variable" calcium fraction and the serum protein content. The constant calcium fraction equals 5.6 mg. As the protein increases, the calcium increment equals 0.56 mg. per gm. of protein. Thus calcium values of about 10.1 and 7.8 mg. respectively may be expected from sera containing 8.0 and 4.0 gm. respectively of protein per 100 cc. of serum.

pressing these relations. The proponents of these equations have indicated plainly that they have a very limited applicability, usually fitting only certain groups of cases. Table 1 shows three of the pertinent formulae that have been evolved.

The original and rather simple formula of Hastings, Murray, and Sendroy (2) applies as well as any to sera normal so far as their calcium and protein content is concerned, and to sera of patients suffering from nephrosis. The formula of Peters and Eiserson (3), which specifically takes into consideration the level of the serum inorganic phosphate, was intended to apply in addition to cases of nephritis. However, as Peters and Eiserson have shown themselves, it does not

apply consistently to such cases. The formula of Gutman and Gutman (4) proposes a correction for the influence of a globulin fraction which is found when the globulin value exceeds 3 gm. per 100 cc. In calculating their formula, they

TABLE 1

Empirical formulae derived from relations of calcium fractions

TOTAL SERUM CALCIUM EQUALS	VARIABLE FRACTION		PLUS	RELATIVELY CONSTANT FRACTION
	Protein × K_1	Phosphorus × K_2		Mainly diffusible calcium
I Hastings, Murray and Sendroy	Prot × 0.56		+	5.6†
II Peters and Eiserson	Prot × 0.556	minus P × 0.255	+	7.0
III Gutman and Gutman	(Alb × 0.8) + (Gl −3)* × 0.2		+	7.0†

* This component is added when globulin is in excess of 3%.

† These formulae are in terms of gm. of protein and mg. of calcium per 100 gm. of serum water; a satisfactory approximation in terms of 100 cc. of serum can be obtained by subtracting (0.05 × protein).

TABLE 2

Applicability of various formulae

I, Hastings, Murray and Sendroy; II, Peters and Eiserson; III, Gutman and Gutman.

ALB	GL	TP	P	NPN	Ca	CALCULATED SERUM CALCIUM (Mg./100 cc. OF SERUM)						DIAG.
Gms./100 cc. of serum			Mg./100 cc. of serum			I	Dev.	II	Dev.	III	Dev.	
3.3	3.0	6.3	17.5	197	6.2	9.1	+2.9	6.0	−0.2	9.2	+3.0	A
2.6	2.3	4.9	4.1	77	6.2	8.1	+1.9	8.7	+2.5	8.7	+2.5	A
4.2	3.1	7.3	7.0	148	10.0	9.3	−0.7	9.3	−0.7	10.0	0	B
4.4	2.1	6.5	6.3	22	6.8	8.9	+2.1	9.0	+2.2	10.1	+3.3	C
4.1	2.9	7.0	2.1	19	6.1	9.2	+3.1	10.2	+4.1	9.8	+3.7	D
4.8	2.0	6.8	2.7	20	7.0	9.2	+2.2	10.1	+3.1	10.4	+3.4	E
3.3	6.9	10.2	2.8	35	10.3	10.9	+0.6	12.0	+1.7	9.8	−0.5	F
4.8	1.9	6.7	4.5	82	16.6	9.1	−7.5	9.6	−7.0	10.4	−6.2	F
4.1	1.8	5.9	1.9	31	14.5	8.5	−6.0	8.7	−5.8	10.0	−4.5	G

Diag.: A, chronic nephritis; B, renal hyperparathyroidism; C, post-op. hypoparathyroidism; D, non-trop. sprue; E, osteomalacia; F, multiple myeloma; G, hyperparathyroidism.

This table compares actual calcium values with those calculated from the various formulae shown in Table 1, the direction of deviation of the actual from the calculated values being indicated by plus or minus.

have excluded cases in which the serum inorganic phosphate level was less than 2.5 or more than 5.0. This formula is then applicable also to instances of hyperglobulinemia in cases of *lymphopathia venereum*.

As stated, the proponents of these various formulae have themselves limited

their application to certain groups of cases. Indeed, one cannot apply these formulae indiscriminately. For instance, if one did, one would find, that in certain groups of cases, the calculated serum calcium value may deviate from the observed value, sometimes quite drastically (Table 2). The discrepancies are significant, however, in so far as they direct attention to the possibility, in an individual case or in certain groups of cases, of: 1) a different calcium-binding power of the proteins; 2) a change in the calcium ion concentration; or 3) a change in both.

We may conclude, then, that such empirical formulae have, in the first place, a theoretical significance in terms of physical chemistry. Furthermore, even though their clinical application is restricted, they have the practical value of making it clear that the complete interpretation of an abnormal serum calcium value in any given case involves the determination of the serum protein and inorganic phosphate and a correlation of these findings with the rest of the picture of the individual case as a whole.

CONDITIONS IN WHICH HYPOCALCEMIA IS OBSERVED

That hypocalcemia is observed, regularly or frequently, in connection with hypoparathyroidism, renal insufficiency, rickets, osteomalacia, and idiopathic steatorrhea and certain other disorders (particularly those involving hypoproteinemia) is common medical knowledge. Let us, then, project the hypocalcemia against the picture of each of these conditions as a whole and consider its meaning in relation to each.

CHRONIC RENAL INSUFFICIENCY

The bare fact of the presence of hypocalcemia in cases of renal insufficiency requires no special emphasis. The initiating and primary factor in the hypocalcemia is phosphorus retention. Sooner or later, some reduction in the total serum protein (and especially in the albumin fraction) likewise becomes a factor. Even though the serum calcium in nephritis may drop to a level at which, in hypoparathyroidism, the patient would develop tetany, it is well known that one rarely observes tetany in nephritis. One reason is that the ionized calcium value tends to remain high enough to keep the neuromuscular junctions from becoming hyperirritable as they are in hypoparathyroidism. In some cases of chronic nephritis, the inorganic phosphate value may be anywhere between 10 and 15 mg. or even more, for long periods of time, while the serum calcium value remains around 7.0 (Table 3). The possible significance of this fact in relation to metastatic calcification will be considered presently.

In connection with chronic nephritis, importance attaches also to the tendency of the parathyroids to undergo alterations. Sometimes they show only evidence of hyperplasia microscopically, but usually they show not only microscopic hyperplasia but gross enlargement. When grossly enlarged, they are usually not more than two or three times the normal size, however, though exceptionally they are huge (cherry-sized, for instance). In association with renal disease, the parathyroid enlargement is due almost entirely to hyperplasia of the chief

cells, the individual cells remaining of approximately normal size. The parathyroid hyperplasia in renal disease has been attributed to the stimulatory effect of phosphate retention and of the consequent disequilibrium of the calcium-phosphorus ratio of the plasma. It is generally held that the parathyroid hyperplasia represents a functional response to the reduced serum calcium level. However, it is not clear, at least to us, why, in some cases of chronic and even protracted renal insufficiency, the parathyroids are only moderately enlarged, while in occasional other cases of this nature they are tremendously enlarged.

Since one does find hyperplasia and enlargement of the parathyroids in association with chronic renal insufficiency, it becomes of interest to consider the bones, for the interrelations between the parathyroids, kidneys, and bones have received a good deal of attention during recent years. In the usual run of cases of chronic renal insufficiency revealing mild or only moderate degrees of para-

TABLE 3

Chronic nephritis

PD	NPN	Ca	P	E	ALB	GLOB	TP
6/16/38	61	7.0	9.5	2.9	2.0	2.7	4.7
7/18	67	6.3	14.6				
8/15	97	6.6	13.6	2.0	2.7	3.6	6.3
8/29	96	8.4	13.5		3.6	3.0	6.6
9/15	100	8.8	13.5	2.3	3.7	3.1	6.8
9/29	95	8.4	11.7		3.2	2.0	5.2
10/26	99	8.6	10.6		3.3	2.3	5.6
11/15	125	7.9	11.3		3.0	2.8	5.8
12/ 7	115	8.0	9.1	1.4	3.0	2.6	5.6

This table shows the pertinent blood chemistry values on different dates in a case (PD) of chronic nephritis in which the phosphorus values remained at very high levels for months. In this case, extensive metastatic calcifications were found at autopsy. In this table and all subsequent ones, E represents the phosphatase activity value, expressed in Bodansky units.

thyroid hyperplasia at autopsy, Doctor Ginzler and one of us (H.L.J.) (5) routinely examined bones from various parts of the body. Our observations in regard to these cases may be summarized as follows: The bones, though usually not altered grossly, often revealed, on microscopic examination, mild but clear-cut fibroporotic changes in the spongiosa. In these cases, the spongy trabeculae showed scattered resorption lacunae containing osteoclasts and connective tissue, and some of them also presented, here and there, deposits of new bone. Occasionally—and specifically when the renal insufficiency had been very protracted —the bones were found even grossly altered. In these cases, the spongiosa was close-meshed and the trabeculae were thickened and distorted so that altogether the skeletal condition amounted to an osteosclerosis. The microscopic observations indicated that the osteosclerosis had developed through gradual accretion of new bone, despite the alternation of reparative with resorptive processes that must have been going on for a long time.

Though there may be some slight degree of parathyroid hyperfunctioning in these cases of renal insufficiency with mild or moderate parathyroid hyperplasia, we think that the slight resorptive changes in the bones, and particularly the sclerotic changes, are best interpretable as having developed on the basis of an acidosis. Indeed, we think that, in the cases showing osteosclerosis, a fluctuating acidosis, in which periods of bone resorption have alternated with periods of bone deposition, provides a better explanation for the bone changes than does hyperparathyroidism, for, as already stated, the parathyroid enlargement in these cases is usually not at all prominent.

On the other hand, in those relatively uncommon cases of protracted renal insufficiency in which the parathyroid hyperplasia and enlargement has become very pronounced, an actual clinical hyperparathyroidism, even registered in typical bone changes, may become engrafted upon the primary renal insufficiency. These cases may be called instances of secondary (renal) hyperparathyroidism, and the following case (Table 4) is one of this type. It represents an instance

TABLE 4

Secondary (renal) hyperparathyroidism

KK	NPN	Ca	P	E	ALB	GLOB	TP
11/10/41	148	10.0	7.0	23	4.2	3.1	7.3
11/13		9.8	7.1	23			
11/24	172	10.1	9.4	26			
12/ 2	171	9.0	7.2	12			
12/ 8	147	9.2	7.9	8.4	3.6	2.1	5.7

This table shows pertinent blood chemistry values in a case of secondary (renal) hyperparathyroidism.

of what may be considered the adult counterpart of the condition which, when found in children or adolescents, is commonly called "renal rickets". The patient was a woman forty-five years of age who was admitted to the hospital because of a glomerulonephritis which, on investigation, proved to be of at least ten years' standing. Though her actual serum calcium values were not above normal (two of them, indeed, being slightly below normal), they were relatively high when considered in relation to her elevated inorganic phosphate values. We know further that all of this patient's parathyroids were of at least cherry size. Nevertheless, in some few cases of secondary renal hyperparathyroidism, the serum calcium values have been found somewhat above the normal level.

Roentgenographically, the patient presented granular mottling of the calvarium, rarefaction of the cortices of the long bones, and more or less annular areas of decreased density representing "brown tumors" and cysts—appearances entirely like those seen in primary hyperparathyroidism (6). The high serum phosphatase activity value is in accord with the extensiveness of the skeletal alterations in this case. In fact, it was only through the history of a nephritis dating back ten years, and the absence of renal calculi as a cause for the renal

insufficiency, that one could be reasonably certain that the hyperparathyroidism had developed on the foundation of primary renal disease.

At this point, a few words in regard to metastatic calcifications seem appropriate. It is well known that in cases of secondary (renal) hyperparathyroidism and in cases of primary hyperparathyroidism with severe renal damage, the arteries may be very heavily calcified. There may also be large patches of metastatic calcification in the subcutaneous tissues, especially around joints, and extensive calcium deposition may occur in certain internal organs likewise—even including the heart. However, metastatic calcifications may likewise be seen in cases of chronic renal insufficiency not associated with more than a very slight degree of parathyroid hyperplasia nor with the bone changes reflecting hyperparathyroidism. We have studied two such cases recently. In both of these cases, the metastatic calcifications seem to be related to the presence, for months, of calcium and phosphorus ions in the blood, in concentrations corresponding to solubility products far in excess of those at which deposition of calcium phosphate may be expected theoretically.

At autopsy, in the case illustrated in Table 3 the parathyroids were found only moderately enlarged and the bones showed only mild resorptive changes. A chronic glomerulonephritis was found, associated with widespread calcification of the arteries. Even the smallest branches of the intestinal arteries were heavily calcified, while, paradoxically enough, the aorta was practically unaffected. There was also calcinosis of the skin and subcutis, extensive calcareous impregnation of the cardiac musculature, and calcium deposition in the kidneys, gastric mucosa, and lungs. Experimentally too, in animals, one can produce extensive calcium depositions by raising to high levels the calcium and phosphorus ions in the blood. The administration of huge and toxic doses of vitamin D or of parathormone also gives rise to metastatic calcifications.

Before we leave the subject of chronic renal insufficiency, a few additional remarks of diagnostic and clinical significance in regard to children may be appropriate. In a child or an adolescent, the presence of unexplained stunting, unexplained acidosis (non-acetone) or unexplained renal disease, separately or together, should suggest the possibility of secondary (renal) hyperparathyroidism, even if no rachitoid lesions are manifest clinically. Furthermore, in any case of so-called "late rickets", no matter how genuine it appears, one should make certain, by searching for renal insufficiency, that one is not dealing with renal hyperparathyroidism instead.

RICKETS AND OSTEOMALACIA

Table 5 shows, for 26 unselected cases of rickets, the initial serum calcium values, arranged in order of increasing magnitude. These cases were of all kinds, involving infants and young children; some had had no antirachitic therapy; some had had inadequate therapy; some were admitted because of tetany, others merely for the correction of bowing deformities, etc. In short, these cases represent the variety of rachitic material which usually accumulates

at hospitals, though the disorder is seen much less commonly now than it was even ten years ago.

The serum calcium value was below 9 mg. in 8 of these 26 cases, between 9 and 10 mg. in 9, and 10 mg. or higher in 9. Thus in only 8 cases was there a

TABLE 5

Rickets—first examination

Ca	P	E	Ca	P	E	Ca	P	E
Ca < 9 mg.			Ca = 9–10 mg.			Ca > 10 mg.		
5.7	5.0	32	9.2	3.6	31	10.0	4.4	15
6.1	6.2	24	9.2	2.0	131	10.1	2.2	126
6.2	3.2	33	9.3	3.0	68	10.2	3.2	191
6.9	3.8	70	9.4	3.0	32	10.3	2.4	39
7.0	3.7	67	9.5	3.9	36	10.3	1.9	21
7.7	3.2	16	9.6	3.1	35	10.4	3.9	42
8.8	1.6	11	9.6	3.1	36	10.6	2.4	50
8.9	2.3	158	9.7	2.4	126	10.6	6.0	18
			9.8	2.9	77	10.7	5.7	119

This table shows the calcium, phosphorus, and phosphatase activity values (E) at first examination in 26 cases of rickets, with the calcium values arranged in order of increasing magnitude.

TABLE 6

Rickets—first examination

P	Ca	E	P	Ca	E	P	Ca	E
P = 3 or less			P = 4 or less			P > 4		
1.9	10.3	21	3.1	9.6	35	4.4	10.0	15
2.0	9.2	131	3.1	9.5	36	5.0	5.7	32
2.2	10.1	126	3.2	6.2	33	5.7	10.7	119
2.3	8.9	158	3.2	10.2	19	6.0	10.6	18
2.4	9.7	126	3.2	7.7	16	6.0	8.8	11
2.4	10.6	50	3.6	9.2	31	6.2	6.1	24
2.4	10.3	39	3.7	7.0	67			
2.9	9.8	77	3.8	6.9	70			
3.0	9.3	68	3.9	10.4	42			
3.0	9.4	32	3.9	9.5	36			
7 of 10 > 50E			2 of 10 > 50E			1 of 6 > 50E		

This table shows these same values in these same 26 cases, but arranged in three groups on the basis of the phosphorus values. The bottom row of each column shows the number of cases, in each group, in which the phosphatase activity value was higher than 50.

definite hypocalcemia; in 9 there was at least a suggestion of it, and in 9 the value was within the normal range. It may be well to point out that, with one exception, the 5 cases showing a calcium value of 7 mg. or less involved infants with well-developed rickets. The exception—a child aged two years with a

calcium value of 6.9 mg.—revealed, through its history, spasmophilia from the age of three months, so that in that case, too, the rickets was already developed in infancy. Of interest also is the fact that the two infants showing the lowest calcium values presented phosphate values around the normal range.

It is more or less generally acknowledged now that the reduction of the serum phosphorus value is a better guide to the diagnosis of rickets and to its severity than is the lowered calcium value. Table 6 shows, in these same 26 cases, the initial serum inorganic phosphate values, arranged in order of increasing magnitude. In 10, the value was 3 mg. or less, in 10 it was between 3.1 and 4 mg., and in 6 it was 4 mg. or higher. The table shows that the lowest phosphorus values are not necessarily associated with the lowest calcium values. However, if one correlates the phosphorus values with the phosphatase values, one can note that the group with the lowest phosphorus values is the one in which the phos-

TABLE 7

Rickets—effects of treatment

'32-'33	MALE, 17 MOS.			'32-'33	MALE, 8 MOS.		
	Ca	P	E		Ca	P	E
2/ 3	9.8	2.7	143†	5/ 9	7.3	3.8	29.3*
2/11		3.2	107	5/17	8.5	4.1	32.2
2/25		4.0	37	5/24		4.8	26.1†
3/23	9.9	5.5	14	6/ 7	9.8	6.1	18.8
4/20		5.9	14‡	6/14		5.0	16.1‡
9/28	10.8	4.9	13	3/13	10.0	5.3	4.9
1/25		5.4	8				

* Viosterol 30 drops.

† 60 drops.

‡ Cod liver oil.

This table shows the effects of treatment on the calcium, phosphorus, and phosphatase activity values in two cases of rickets.

phatase values are highest. Indeed in 7 of the 10 cases showing phosphorus values of 3 mg. or less, the phosphatase value was 50 units or higher, and we have found that in a rachitic infant or child presenting such a phosphatase value the rickets is generally severe. Furthermore, as examination of Table 5 will show, there is no correlation between the level of serum calcium and serum phosphatase activity.

The phosphatase value is not only a good index of the severity of the rickets, but usually also a better guide to the adequacy of the antirachitic treatment and a more accurate indication of the complete abolition of the rachitic state than the calcium value or even the phosphorus value. Specifically, as illustrated by Table 7, taken from previously published data (7), the phosphorus value is likely to rise promptly even under somewhat inadequate treatment, while the phosphatase value responds much more slowly and does not reach the normal level in its fall until the healing of the rickets is really complete.

The parathyroids are very likely to undergo some degree of enlargement in cases of rickets. There seems to be no doubt that this is a functional response to the tendency of the serum calcium to be lowered in this disease. There are some investigators who hold that, subordinately to vitamin D deficiency, parathyroid hyperfunctioning plays a role in the evolution of the osseous changes. It seems to us that the validity of this point of view can be questioned on several grounds: 1) the parathyroids do not regularly undergo enlargement in rickets; 2) one can produce experimental rickets in parathyroidectomized young rats put on a low phosphorus-high calcium regimen; and 3) when parathyroid enlargement is present, it represents a physiological adaptive response. Indeed, within physiologic limits, it might even be regarded as a beneficial influence somewhat in the manner of the hypertrophy of the anterior lobe of the pituitary in pregnancy, the hypertrophy of the cortex of the adrenals in cases of chronic infection, or the hypertrophy of the islands of Langerhans in infants born of diabetic mothers.

We turn now to adolescent rickets and osteomalacia. We all know that adolescent rickets is by no means as common in the United States at present as it was twenty or thirty years ago. Indeed, as already pointed out, when one does see an instance of what appears to be adolescent rickets on the basis of the x-ray appearances of the bones, the chances are that one is dealing with chronic renal insufficiency of childhood with skeletal changes—that is, renal rickets. Another possibility is that the case is one of idiopathic steatorrhea with skeletal changes.

Genuine osteomalacia of adults—that is, osteomalacia of calcium deprivation and added vitamin D deficiency—has always been rare in this country. This is the osteomalacia which is associated with repeated pregnancy or pregnancy of young girls and which is still endemic in parts of China and India. Occasionally, in this country, we do encounter a sporadic instance of non-puerperal bone softening which simulates genuine osteomalacia anatomically but is rather refractory to the usual treatment (that is, high calcium diet and high vitamin intake) for this condition. In these cases, the serum calcium value is low. At any rate, the significance of these cases is by no means clear.

CERTAIN OTHER CONDITIONS INVOLVING HYPOCALCEMIA

As Table 8 shows, hypocalcemias are occasionally observed also in connection with cachectic states developing in relation to malignancy, and with non-tropical sprue. In cases showing nutritional hypoproteinemia and a consequent low calcium value, there need not be any significant osteoporosis. In cases of non-tropical sprue, the hypocalcemia is usually associated with an osteoporosis. This is so because much of the dietary calcium combining with the fatty acids in the stools fails to be absorbed and a calcium deprivation results.

One must point out, however, that in cases of menopausal osteoporosis devastatingly severe thinning of the bones may occur while the serum calcium value almost always remains within normal limits. This merely points to the fact that in these cases there is no disturbance in the absorption of calcium, no hyper-

activity of the parathyroids to draw the calcium out of the bones, and no vitamin D deficiency, and that, as is becoming increasingly clear, the cause of the osteoporosis in this condition is to be sought elsewhere. Perhaps it is an exaggerated manifestation, in the skeleton, of the post-menopausal involutional processes going on in the body as a whole.

HYPOPARATHYROIDISM

As is well known, hypoparathyroidism in man ensues most often upon the accidental removal or injury of parathyroids in the course of subtotal thyroidectomy. There are also cases of so-called "idiopathic" hypoparathyroidism, occurring both in children and in adults. Interestingly enough, the manifestations in these cases are usually exacerbated in the winter time and may even be limited

TABLE 8

Certain other hypocalcemias

ALB	GLOB	TP	Ca	P	E	DIAG.
4.1	2.1	6.2	8.7	3.6	11.0	Cach. malig.
2.4	2.3	4.7	8.0	3.3	3.3	Nutr. hypoprot.
3.3	2.2	5.5	8.7	4.1	2.7	Anem. hypoprot.
2.2	2.9	5.1	7.8	1.8	10.8	Non-trop. sprue
4.6	2.4	7.0	5.8	2.8	5.6	Non-trop. sprue
4.4	2.6	7.0	8.5	3.1	3.1	Non-trop. sprue
4.8	2.0	6.8	6.9	2.6	13.5	Osteomalacia
			Menopausal osteoporosis			
4.3	2.9	7.2	9.5	3.1	7.8	

This table illustrates typical blood chemistry values for some other conditions involving hypocalcemia. Appended are the figures for a case of menopausal osteoporosis, in which, as usual in this condition, no hypocalcemia was observed, though the skeleton had become extremely porotic.

to this period. We know very little about the pathology of the parathyroids in the cases of so-called "idiopathic" hypoparathyroidism, except that there is a record of one case which, at autopsy, showed complete fatty replacement of all four parathyroids (8).

The clinical manifestations in the cases of surgical parathyroprivia are known to begin within two or three days, as a rule, after the operative intervention. They are set going and maintained by the drop in the serum calcium level. In some patients, evidences of increased neuromuscular excitability will already be apparent when the serum calcium value is only slightly under 7 mg., and they are likely to be quite pronounced if it is under 6 mg. The drop in the serum calcium level is, of course, associated with a rise in the serum inorganic phosphate level, but there can be no doubt that the latter change lags behind the former. In regard to the hypocalcemia, it is important to note that the drop in the ionized fraction of the calcium is disproportionately large.

If the degree of damage or loss of parathyroid tissue is not severe, the postoperative manifestations of parathyroprivia may rapidly vanish. If, on the other hand, the damage or loss of parathyroid tissue is pronounced, a chronic hypoparathyroidism with a whole complex of associated manifestations (trophic and other) may set in and be difficult to control. The relation of the hypocalcemia to certain of the trophic and other disturbances seen in these cases is not entirely plain. We do know, however, that in disorders associated with hypocalcemia of long standing, even when its basis is not hypoparathyroidism, one can get cataracts as one does in chronic hypoparathyroidism.

CONDITIONS IN WHICH HYPERCALCEMIA IS OBSERVED

Hypercalcemia, to which we now turn, is observed, regularly or frequently, in connection with hyperparathyroidism and multiple myeloma. Very rarely, one observes it in a case of carcinoma extensively metastatic to the skeleton and possibly also in a case of leukemia with extensive skeletal changes.

TABLE 9

Hyperparathyroidism

FF	Ca	P	E	NPN	ALB	GLOB	TP
7/ 7/39	14.5	1.9	4.5	31	4.1	1.8	5.9
7/10	14.4	1.8	4.5	28	4.3	1.6	5.9
8/ 3	15.7	1.9	4.4	39	4.4	1.6	6.0
11/ 8	15.3	2.0	6.7	29			
4/23/40	14.2	2.2	6.5	32	4.4	2.0	6.4
10/30	14.1	1.9	7.6	28			
12/ 5	Mediastinal para. (400 mg.) removed						
5/24/41	9.3	3.2	2.7				

This table shows the pertinent blood chemistry values on various dates in a case of primary hyperparathyroidism presenting the typical hypercalcemia and hypophosphatemia and an only slightly increased phosphatase activity.

HYPERPARATHYROIDISM

Early in the development of our current conception of hyperparathyroidism it was already noted that hypercalcemia and hypophosphatemia are expected findings in the disease. In a general way, this observation is still valid, but it fails to fit cases in which a renal factor, and specifically renal insufficiency, is part of the picture.

The significance of the serum calcium and phosphorus values in the diagnosis of hyperparathyroidism can perhaps be brought out best by discussion of figures on a few typical cases. It seems only proper to discuss first a case showing particularly clearly the characteristic hypercalcemia and hypophosphatemia. (Table 9). The patient was a woman fifty-four years of age who had been suffering for almost three years from various aches and pains, intractable constipation, and frequent bouts of nausea and vomiting before a parathyroid adenoma was found and extirpated. Early in the course of her illness, her left kidney was removed because of the presence of calculi and pyonephrosis, but the

fact that she was suffering from hyperparathyroidism was not recognized at that time. Subsequently, she came under the observation of Doctor Milton Kissin of New York City who, suspecting this condition, had us analyze her blood with this in mind. Indeed, we had the opportunity of examining her blood several times and of correlating the chemical data with the clinical course and the roentgenographic bone findings over a period of fifteen months. It can be seen that the patient presented a definite and consistent hypercalcemia and a correspondingly definite and consistent hypophosphatemia. Her non-protein nitrogen values were always within normal limits. Her total protein values were slightly low. From the blood chemistry findings in this case, one can therefore draw the inference that the ionized calcium fraction was increased. Such an increase would explain the hypotonia observed in cases of hyperparathyroidism.

It should be pointed out that her serum phosphatase activity was never strikingly elevated. It was only 4.5 Bodansky units (very slightly above the normal limit) during the early course of our observation of her and reached only

TABLE 10

Hyperparathyroidism

SB	Ca	P	E		Ca	P	E
1/13/41	11.2	2.6	4.6	2/26/41	8.6	2.5	4.9
1/20	12.1	3.3	4.7	3/ 3	9.5	3.2	5.3
2/20	11.9	2.6	6.3	3/ 5		3.4	5.3
2/24	11.4	2.7	6.1	3/ 6	10.1	3.5	5.3
2/24	Para (2.2 gm.) removed)			3/13	10.2	3.9	4.6

This table shows the pertinent blood chemistry values in another case of primary hyperparathyroidism.

7.6 in its subsequent rise. This finding is in harmony with the fact that roentgenographically the patient's bones presented only a slight degree of porosis. This mildness of the bone changes, reflected also in the absence of any striking increase in the serum phosphatase activity, likewise accounts for the fact that when the offending parathyroid adenoma (which weighed only 400 mg.) was finally found in the mediastinum and removed, the postoperative hypocalcemia was not severe or prolonged. Furthermore, it was associated with only ephemeral and easily controllable hypocalcemic phenomena. Specifically, there was tingling and numbness of fingers and toes on the third day after operation, and a positive Chvostek which appeared on the fourth day was already gone on the seventh day.

The chemical and roentgenographic findings and the postoperative course in this case are in line with those to be noted now (Table 10). These relate to a woman fifty-four years of age, whose first clinical manifestation of hyperparathyroidism was the passage of renal calculi. She presented only a mild degree of hypercalcemia, a doubtful hypophosphatemia, a slight rise in serum phosphatase activity, a normal non-protein nitrogen value, and a roentgenographic bone picture which might pass superficially as normal. Removal of a para-

thyroid adenoma, 2.2 gm. in weight (from the neck) was not followed by any hypocalcemic postoperative phenomena, and ten days after the operation the patient's serum calcium was within normal limits.

There can be no doubt that, as a rule, the more severe the bone changes and the higher the phosphatase activity, the more severe, prolonged and difficult to control are the postoperative hypocalcemic phenomena following removal of the offending parathyroid tissue. The simplest and most plausible explanation for this state of affairs is that when the condition of hyperparathyroidism is corrected, the depleted skeleton represents a sort of "vacuum" which greedily sucks in for repair considerable circulating calcium, thus tending to create a prolonged postoperative hypocalcemia. It is of interest in this connection that in guinea pigs whose bones have undergone demineralization from repeated injections of parathormone one can demonstrate that a hypocalcemia appears as early as two days and may persist for two weeks after the injections are stopped. To illustrate this point, we are showing the already published table of a single experiment (Table 11), whose results we explained as follows: The repeated injection of parathormone reduces the calcium reserves of the bones, and, upon discontinuance of the parathormone, calcium is reabsorbed into the bones at such a rate as to cause hypocalcemia (9).

For purposes of contrast, let us now trace the postoperative course in a case of hyperparathyroidism with pronounced bone changes and a corresponding high serum phosphatase activity value (Table 12). The patient was a man forty-nine years of age who was hospitalized because of a fracture through the middle of the shaft of a humerus. He also presented a kyphoscoliosis, bowing deformities of his lower limbs, and a swelling of the lower jaw, all attributable to advanced bone changes of hyperparathyroidism. Furthermore, his calvarium showed granular mottling in the x-ray picture. In this case, postoperative hypocalcemia and hypocalcemic phenomena were still in evidence for at least two and one-half months after the operation. Indeed, hypocalcemic phenomena were present much longer, although we have no chemical determinations for this subsequent period. We do know that one year after the operation the patient's serum calcium value was normal, and that it was not until many months later that the serum phosphatase value had also become normal.

In the case, seen through the courtesy of Doctor Ottenberg, of a man of middle age suffering from primary hyperparathyroidism associated with pronounced enlargement of all four glands, the postoperative hypocalcemia and hypocalcemic phenomena were very protracted and exceedingly difficult to control. In this case, the patient had had a renal calculus removed several years before he came to Doctor Ottenberg, and his hyperparathyroidism was probably already present at the time of that operation. Doctor Garlock corrected the hyperparathyroid state in a two-stage operation, removing two large cherry-sized glands at one session and the third and about three-quarters of the fourth at another. In such a case, the surgeon is really confronted by a dilemma, for if too much parathyroid tissue is left behind, there is great likelihood of recurrence of the hyperparathyroidism with regrowth of the remaining tissue. On the other

hand, there is danger of the development of intractable hypoparathyroidism if too little is left behind. Actually, in this case, for fourteen months subsequent to his second operation, the patient had hypocalcemia and hypocalcemic phenomena which were exceedingly difficult to control despite heavy medication. At the present time, this man's serum calcium, phosphorus, and phosphatase ac-

TABLE 11

Effect of parathormone administration

WEIGHT AT END OF EXPERIMENT	DAYS AFTER LAST INJECTION	SERUM Ca	SERUM P
gm.			
480	4	9.4	7.7
400	4	8.0	8.0
480	4	7.4	7.8
350	5	7.6	8.4
370	5	8.8	4.8
370	7	10.2	6.9

In guinea pigs, young and adult, the serum calcium value normally lies within the range 10.5 ± 0.5 mg. per 100 cc.

Serum inorganic phosphorus values vary from about 8.0 mg. per 100 cc. for very young guinea pigs to about 3 mg. for adult guinea pigs.

This table shows the appearance of hypocalcemia in guinea pigs, some days after cessation of injections of parathormone, which had been given over a considerable period of time.

TABLE 12

Hyperparathyroidism

JG	Ca	P	E		Ca	P	E
2/14/38	13.0	2.7	23	4/ 6/38	5.6	4.3	5.2
2/25	14.0	3.0	22	4/18	5.9	4.0	3.5
2/26	Para (13 gms.)		removed	4/25	6.2	4.0	3.7
2/28	8.4	2.4	18	5/16	8.0	3.4	4.8
3/ 8	5.4	2.8	20	3/ 3/39	10.2	2.9	4.4
3/14	5.8	3.2	12	5/24	10.1	3.1	4.7
3/22	5.2	4.3	6.6	7/18	9.7	3.1	4.9
3/28	5.0	5.1	5.8	3/27/41	9.8	2.5	2.2

This table shows pertinent blood chemistry values in a case of hyperparathyroidism in which the phosphatase activity value (E) was much increased and in which the skeleton was very much modified. In this case, postoperative hypocalcemic phenomena persisted for months and were difficult to control.

tivity values are normal, being respectively 9.4, 4.2, and 3.3, and his bones have undergone extensive healing. However, he now has bilateral renal calculi and is also showing evidences of renal insufficiency, his non-protein nitrogen being 61 mg. per cent. Indeed, although the hyperparathyroidism has been abolished, the prognosis in this case is grave unless an attempt now to correct the renal status is successful. This case shows again how difficult the treatment and control of some cases of hyperparathyroidism may be.

MULTIPLE MYELOMA

In multiple myeloma we have another disease in which there is very likely to be a hypercalcemia. Furthermore, as is also well known, one often finds a hyperproteinemia in this disease. The following table (Table 13) of single determinations, in some of our more recent cases, all confirmed by biopsy or autopsy, shows representative findings. In six of the seven cases in which calcium determinations were made there was a hypercalcemia. When there is a hyperproteinemia it is the globulin fraction, and often the euglobulin, or some

TABLE 13

Multiple myeloma

	Ca	P	E	NPN	ALB	GLOB	EUG	TP	BJP
MM	10.3	2.8	2.4	35	3.3	6.9	5.5	10.2	Neg.
AR	11.7	3.8	3.5	22	2.8	3.4		6.2	Pos.
MH	12.3	4.2	1.8	31	3.0	6.3	0.2	9.3	Neg.
PL	12.5	5.2	2.3	51	2.7	10.1	7.1	12.8	Pos.
CJ	16.6	4.5	5.1	82	4.8	1.9	0.5	6.7	Neg.
EC	17.8	4.4	2.5	61	4.1	2.8	0.9	6.9	Neg.
JM	14.1	5.3	2.6	57					Pos.
JB				107	2.0	14.0	11.3	16.0	

This table shows blood chemistry values in 8 individual cases of multiple myeloma. Phosphatase activity value (E), euglobulin value (EUG), Bence-Jones protein (BJP).

TABLE 14

Multiple myeloma

MH	Ca	P	E	NPN	ALB	GLOB	EUG	TP	BJP
1/15				37	3.0	4.9		7.9	
1/20	12.3	4.2	1.8	31	3.0	6.3	0.2	9.3	Neg.
1/28	16.3	3.9	3.1	41	3.2	7.2	0.3	10.4	
2/11	13.6	3.2	3.2	54	2.8	7.6	0.1	10.4	
2/19	12.4	2.2	3.2	52	2.9	7.4		10.3	Neg.

This table shows the pertinent blood chemistry findings in one of the cases of multiple myeloma, on different dates. A hypercalcemia is present. In spite of a hyperglobulinemia, the euglobulin fraction is not increased.

other protein fraction precipitated with and usually determined as "euglobulin," that is increased. An increase in the globulin fraction seems generally to be associated with a lowering of the albumin fraction. However, in an individual case, if the albumin fraction was within the normal range, the globulin fraction tended to be also within this range.

Let us consider now the figures in two cases in which repeated examinations have been made at relatively short intervals. (Tables 14 and 15). In one of these cases, though there is a consistent hypercalcemia, an additional pronounced rise in the calcium value appeared at one time. In addition, though

the globulin fraction is strongly increased, the euglobulin has remained within the normal limits. In the other case, the hypercalcemia was very striking, the serum calcium value ranging between 16 and 17 mg. for a period of about a month, though it then dropped somewhat. Furthermore, in this case the globulin fraction is not increased, and the euglobulin fraction seems to be only slightly raised. Finally, it should be pointed out that in both of these cases (which, incidentally, showed pronounced skeletal alterations) repeated examinations showed consistent absence of Bence-Jones proteinuria.*

It seems clear that the presence of hypercalcemia in multiple myeloma cannot be attributed to hyperproteinemia. One could think that it results merely from the mobilization of calcium from the skeleton in the process of resorption of the osseous tissue by the growing myeloma tissue. At any rate, we cannot inculpate

TABLE 15

Multiple myeloma

CJ	Ca	P	E	NPN	ALB	GLOB	EUG	TP	BJP
12/12	16.6	4.5	5.1	82	4.8	1.9		6.7	Neg.
12/15	17.0	4.0	4.3	76	4.4	2.2	0.8	6.6	Neg.
12/24	16.0	3.2	8.0	44	4.4	2.2	0.5	6.6	
1/ 7	17.1	3.5	8.8	56	4.3	2.2	0.5	6.5	Neg.
1/19	16.3	3.3	9.7	49	4.3	2.2	0.5	6.5	Neg.
2/16	14.4	3.4	9.9	42	4.6	1.8	0.5	6.4	
3/ 9	15.1	2.3	8.4	38	4.4	1.7	0.5	6.1	Neg.

This table shows the pertinent blood chemistry values in another case of multiple myeloma on different dates. A hypercalcemia is present. In this case, though there is *no* hyperglobulinemia, the euglobulin fraction is slightly increased.

hyperfunctioning of the parathyroid glands in the hypercalcemia. In fact, in several of our cases of multiple myeloma with hypercalcemia which subsequently

* The patient referred to in Table 15 survived for about 9 months after the last entry in this table. During this interval, 13 additional sets of chemical determinations on his blood were made. These showed an irregular decline of the total protein value to 5.0 mg. The loss was mainly in the albumin fraction, but the A/G ratio remained within the normal limits of 2 to 2.5. The euglobulin value (which was determined only a few times) remained only slightly above normal throughout. During all this time, the patient continued to show a hypercalcemia, the calcium value ranging between 14.8 and 17.0 mg. until two weeks before death, when it was only 13.1 mg. On one occasion, also, Doctor D. Moore of the Dept. of Anatomy at Columbia University carried out an electrophoretic study on this patient's blood. This showed that the albumin-globulin ratio was normal and that there were no abnormal proteins (including Bence-Jones protein) in the serum. At autopsy, which confirmed the diagnosis of multiple myeloma, specimens of both pleural fluid and bone marrow tumor tissue were taken, in a search for abnormal proteins. However, neither the ordinary chemical methods nor electrophoretic methods revealed any such proteins (including Bence-Jones protein). Furthermore, Bence-Jones protein continued to the end to be absent from the urine of the patient. The question of why some cases of multiple myeloma show abnormal proteins in their blood and urine while others do not, presents an interesting problem.

came to autopsy, specific study of the parathyroids showed that they were of normal size and certainly not hyperplastic even microscopically.

Aside from the diagnostic significance of Bence-Jones proteinuria in multiple myeloma, we need not concern ourselves here with the many questions relating to the protein or, more accurately the proteins, in question. If found in the urine, Bence-Jones protein already points very strongly to multiple myeloma, and if it is found with a hypercalcemia or hyperproteinemia or both, the evidence in favor of multiple myeloma is practically conclusive. Indeed, the chemical findings often direct attention to the presence of multiple myeloma at a time when the x-ray findings in the case are equivocal or even inconsistent with the general conception of the x-ray picture of this disease.

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PROCEEDINGS OF SEMINARS

ON

RECENT ADVANCES IN BACTERIOLOGY AND IMMUNOLOGY WITH CLINICAL CONSIDERATIONS

Under the Auspices of the Department of Bacteriology, The Mount Sinai Hospital

GREGORY SHWARTZMAN, M.D., *Chairman*

Wednesday, March 4, 1942

1. Immunization in Rickettsial Diseases. *Saul W. Jarcho, M.D.*

The present world-wide conflagration threatens a sharp increase in the prevalence of all three of the varieties of rickettsial disease—the typhus group, the spotted fevers, and the diseases related to Japanese river fever. There is much evidence that typhus has raged in central and eastern Europe during the present season but exact statistics are not available.

Against typhus several types of vaccine have been devised. In this country the use of live vaccine has found little favor. Weigl's method, which requires for preparation intrarectal injections of lice with rickettsiae, is unsuitable for the production of large quantities, although the vaccine itself is probably useful. Much more satisfactory for present needs is the technique of Ruiz Castaneda. By this method viable rickettsial suspensions are injected intranasally into mice and rats. A rickettsial pneumonia ensues, the microörganisms being present in enormous numbers. The War Department, in a circular letter dated January 6, 1942, gave official approval to the Cox technique, in which the rickettsiae are grown in the yolk sac of the chick embryo and the subsequently formolized and titrated material is used for vaccination.

2. Passive Serum Sickness. *Samuel Karelitz, M.D.*

The report deals with patients convalescing from serum sickness due to injections of horse serum. Their sera, possessing anti-horse antibodies, are termed human anti-horse sera. If 2–10 cc. of a human anti-horse serum are injected intravenously into patients who received injections of therapeutic horse serum 1–8 days before, a reaction is produced within a few minutes which is milder than, but otherwise similar to serum sickness. This reaction may be localized at the site of horse-serum-injection or may appear as a generalized urticaria. This phenomenon was named "Inverse Serum Sickness" by Voss, who first called attention to it. Karelitz suggested that it may be more appropriately called "Passively Acquired Serum Sickness" or just "Passive Serum Sickness".

Voss claimed that an episode of passive serum sickness prevented the normal serums reaction in 35 out of 36 cases. Although failing to corroborate this claim, Karelitz observed, however, that an episode of passive serum sickness altered the subsequent course of actively acquired serum sickness in horse serum

treated children. In addition to the above, the following facts were also studied by him.

Demonstration of antibodies to horse serum by localized passive serum reaction. If an individual is prepared by an intradermal injection of 0.1 cc. of horse serum, and 8 hours later receives an intravenous injection of 2–10 cc. of antihorse serum, urticaria appears at the prepared skin site. In this manner antibodies for horse serum were demonstrated in 9 out of 10 human antihorse sera. Voss believes, however, that all antihorse sera without exception produce this reaction.

Demonstration of antibodies to horse serum by passive transfer and by skin tests. Where normal skin is prepared with horse serum, the prepared sites react to antihorse serum locally injected 48 hours later. The same reaction is successfully produced when the normal skin is prepared with the human antihorse serum and then tested 48 hours later with horse serum.

Since the skin, like other tissues of an individual recently treated with horse serum, probably contains residual horse serum, an intradermal injection of human antihorse serum should and does produce an urticarial reaction. The intensity of skin reaction is inversely proportional to the skin reaction to horse serum, being positive 1–2 days after treatment with horse serum and becoming smaller after 6, 7, or 8 days, or at the time when the skin shows symptoms of serum sickness. Ten antihorse sera studied varied in their ability to produce this skin reaction.

Antibodies in human antihorse sera. The antihorse sera studied contained precipitating heterophile, antibodies and antibodies capable of passive transfer, however, not all antibodies were represented in every serum. The production of passive serum sickness did not seem to be directly related to the presence of any heretofore indentified antibodies. Nevertheless, Passive Serum Sickness is specifically a reaction of horse serum treated individuals to antihorse serum.

In much of this work the author was assisted by Dr. Stephen S. Stempien, Dr. Aram Glorig, and Dr. Samuel Spector, former Residents at the Willard Parker Hospital.

3. Inclusion Blenorrhea. *Herbert Katzin, M.D.*

Recent researches on inclusion-blenorrhea are likely to be of far-reaching importance in virus bacteriology.

The disease is characterized by acute or subacute inflammation in the epithelium of the conjunctiva, the urethra or the transitional zone of the cervix in humans, baboons, and Macacus Rhesus monkeys. Infectivity is low, healing is spontaneous and complete after a course of several months, without scarring, and without development of immunity. The usual modes of transmission are venereal in nature.

The virus is filterable, closely related to trachoma and lymphogranuloma venereum, with the following features in common: the inclusion bodies are basophilic, large in size, stain easily with Giemsa, and are not preserved by glycerin. The virus undergoes life cycles, progressing from the initial forms to elementary bodies. These agents seem to be the only viruses which respond to sulfonamides.

Inclusion blenorrhea virus has not been cultivated outside of the living animal, nor has it been preserved for any length of time *in vitro*; although extreme dry cold seemingly protects it against deterioration. Studies on propagation of the virus with the use of embryonic epithelium suggest themselves.

4. Etiology of Influenza-like Diseases Illustrated by a Recent Institutional Outbreak. *Jonas Salk, M.D.*

Certain recent advances in the study of virus diseases are of interest to the clinician. To illustrate this, the methods employed in the identification of the causative agent of a local outbreak of influenza in the course of the winter epidemic of 1940–1941 are described. The significance of the negative findings in two cases which occurred during the epidemic, and in two sporadic cases occurring two months later is also discussed.

In the middle of January, 1941, there appeared suddenly and almost simultaneously among the interne staff, nurses and employees of The Mount Sinai Hospital, an illness which was diagnosed clinically as influenza. Fourteen cases of varying severity were studied. In the laboratory of Dr. Thomas Francis, Jr., then at New York University College of Medicine, and agent identified as a Type A influenza virus was isolated from the pharyngeal washings of one of the patients, by intranasal inoculation of ferrets. In another ferret, inoculated with the washings from a second patient, serological evidence of Type A influenza virus infection was obtained. Blood serum taken in the acute and convalescent periods, was tested for complement-fixing and virus-neutralizing antibodies specific for Type A and B influenza viruses. In the fourteen cases there was a rise in the Type A influenza antibody titer, but not in the Type B. In two other cases in which there were x-ray findings of pneumonia, and which appeared to be cases of severe influenza with pneumonitis, no evidence was obtained that these were due to the influenza virus. In retrospect, these were probably cases of "atypical pneumonia" due to some other agent. Two months later, there occurred two cases of an influenza-like illness, not due to the influenza virus.

From this study it appeared that we were dealing with three types of influenza-like diseases, all due to different etiologic agents. First, epidemic influenza, caused by the Type A influenza virus; second, cases of atypical pneumonia occurring in the course of an epidemic of influenza and caused by some other agent; third, sporadic cases of an influenza-like disease, due to some agent other than the virus of epidemic influenza.

5. Surgical Bacteriology. *Gabriel P. Seley, M.D.*

A careful bacteriologic survey of neoplastic and inflammatory lesions of the gastro-intestinal tract was made in order to study postoperative peritonitis from its inception. Streptococci of all varieties, B. coli and B. Welchii when found each alone or in combination in the gastro-duodenal lesions, were of particular significance since these cases were associated with a comparatively higher incidence of wound and intra-abdominal infections. The finding of B. Welchii was clinically unexpected and always indicated a grave prognosis. In the colonic

group of cases an opportunity was offered to compare the bacteriologic flora before and after administration of sulfanilamide. There was a striking diminution of the number of streptococci and B. Welchii in cases treated preoperatively with sulfanilamide. These observations suggested the use of sulfanilamide preoperatively. The mortality rate from peritonitis in 123 colon and rectal operations thus treated was 4 per cent against 10 per cent mortality reported in the literature.

Wednesday, March 18, 1942

6. A Toxic Ocular Reaction: New Property of Shwartzman Toxins. *Corrado Ajo, M.D.*

A primary ocular reaction to the intravenous injection of the Shwartzman toxins[1] was observed in rabbits. The reaction consists of irido-conjuntival hyperemia and, upon removal, coagulation of the aqueous humor. It is accompanied by miosis, photophobia, and lacrimation, and an increased permeability of the ciliary bodies to fluorecein. A strong Tyndall phenomenon is visible in the anterior chamber in the beam of the Slit lamp. This toxic ocular reaction appears several minutes after the intravenous injection of toxins, reaches a maximum intensity in a few hours, and is notably reduced or completely disappears about twelve hours later. The smallest amount of toxins injected intravenously which induces aqueous humor coagulation is termed "the minimal coagulation dose." (MCD)

The reaction may be also produced by way of intra-arterial and intraperitoneal routes as well as by injection into an highly vascularized area of the skin (lateral third of the ear surface). Rabbits fed with large amounts of toxin fail to show any ocular reaction. Protection against the ocular reaction is obtained by previous intradermal or intravenous preparation of rabbits with the Shwartzman toxins or by moccasin snake venom injection.

Toxins preserve their potency for several months when undiluted preparations are stored in the refrigerator. The toxic ocular principles do not pass through dialyzing membranes, show resistance to high temperatures (i.e. 120°C. and above), are definitely weakened by the addition of formalin, and are specifically neutralized by Shwartzman antitoxins.

The toxic ocular reaction is also obtained in cats and dogs but fails to appear in other usual laboratory animals, including guinea pigs which produce the Shwartzman phenomenon only in a certain percentage.

The toxic ocular reaction was obtained in approximately 95 per cent of a large number of rabbits injected intravenously with 10 or more minimal coagulating doses of toxin per kilo of body weight. Thus the reported reaction represents a new property of the Shwartzman toxins, demonstrating their marked primary toxicity for the ocular tissues of rabbits.

[1] Soluble inorganic bacterial products derived mainly from Gram-negative microörganisms and producing in rabbits severe damage at the site of local injection only following subsequent intravenous injection (Shwartzman phenomenon).

7. The Diazonium Compounds (Landsteiner) and Their Clinical Application. *Isadore E. Gerber, M.D.*

Successful attempts at modifying the antigenic properties of proteins by nitration or iodination in 1903 by Obermayer and Pick, subsequently led Landsteiner to attempt similar studies with proteins conjugated with various organic chemicals. In a long series of experiments, from 1917 to date, he was able to demonstrate that proteins, conjugated with various organic chemicals by means of the well known diazonium reaction, were antigenically specific and that the specificity was directed towards the azocomponent, the protein fraction serving only as a carrier. The specificity of the azoproteins was adequately demonstrated by various serologic methods including the precipitin test, complement fixation, desensitization to, or production of anaphylactic shock. Specific union of the azocomponent *per se* with the homologous antibodies was also demonstrated. Other investigators, and Landsteiner in further studies, found that animals could be specifically sensitized to various chemicals under certain conditions. These conditions indicated that the chemical antigen possibly united with the animal body proteins to produce a sensitizing azoprotein so that subsequent contact with the antigen *per se* resulted in a contact-dermatitis, as seen in humans. These experiences lead one to believe that the mechanism underlying human hypersensitivity might well be similar to, or identical with, experimental anaphylaxis. Therapeutically, azoproteins might be used for desensitization in human cases when the offending chemical antigen is known.

8. Bacteriology of Nose, Sinuses and Nasopharynx. *Joseph L. Goldman, M.D.*

Bacteria of low pathogenicity such as Staphylococcus albus B and diptheroids are usually found in the normal nasal flora in sparse numbers. Although less frequently, the Staphylococcus aureus A and Streptococcus viridans may be present in the nasal flora without any evidence of infection. The microörganisms isolated from cases of evident nasal and sinus infections are, as a rule, pneumococci, Streptococcus hemolyticus (Beta), Staphylococcus aureus A, Streptococcus viridans (Alpha) and, more rarely, Streptococcus non-hemolyticus (Gamma), B. influenza and B. Friedlander. In acute and subacute infections, there are frequently encountered pure cultures of a single pathogenic microörganism.

When sinus washings are obtained under certain precautions, the paranasal sinuses are shown to be sterile in the absence of an infection. The finding of a small amount of flakes in sinus washings, as brought out by our studies under progress, must be considered as questionable evidence of sinus infection. Stained spreads of these flakes show cellular elements but rarely any microörganisms. The microörganisms obtained on culture are those usually present in the normal nose. The sinuses, however, containing purulent clumps and large amounts of secretion, from which pathogenic bacteria are consistently isolated, must be considered infected, even in the absence of significant local symptoms.

The nasopharyngeal flora differs from the nasal flora in the following respects, namely: several microörganisms are cultured simultaneously; the Streptococcus

viridans (Alpha) and Streptococcus hemolyticus (Beta) are frequently present in the absence of infection. The latter microörganisms may evidently exist in the nasopharynx without invading the nose.

9. Histamine and Histaminase. *Sheppard Siegal, M.D.*

Histamine is a powerful pharmacologic agent widely distributed in the body. The histamine theory of anaphylaxis postulates liberation of histamine as a result of the interaction between an antigen and an antibody in the tissue. Strong evidence exists that release of histamine during anaphylaxis takes place only in some animal species (guinea pig, dog) but not in others (horse, calf). Incidental liberation of tissue substances other than histamine helps to explain some of the minor phenomena of anaphylaxis. Thus, heparin release accounts for the incoagulability of the blood, characteristic of canine anaphylaxis, etc.

The role of histamine in human allergy is more controversial. Blood histamine studies in allergic disease by the bio-assay method are inconclusive and other evidence is conflicting. Histamine "desensitization" presupposes the development of histamine tolerance following the administration of increasing doses of this substance. However, the evidence from animal experimentation provides only equivocal support for this assumption. The results achieved with this form of histamine treatment must, therefore, be interpreted with caution.

Histaminase is the term applied to the ability of certain animal tissue extracts, especially those of kidney, to inactivate histamine *in vitro* on prolonged incubation. There is suggestive evidence that histaminase belongs to the class of enzymes. The theoretical basis of histaminase therapy rests on the assumption that it acts *in vivo* to detoxify histamine. However, no sound physiologic basis appears to exist at present in clinical use of histaminase. This point of view is further borne out by a critical evaluation of the clinical results so far achieved with histaminase therapy.

10. Bactericidal Agents with Special Reference to Gramicidin. *Emanuel B. Schoenbach, M.D.*

An ideal bactericidal agent should have low toxicity for tissues. Numerous extracts of bacteria have been made, possessing bactericidal action (Wakesman, S. A.: Bacteriology Review, 5: 231, 1941). These extracts have all been general protoplasmic poisons and not suitable for clinical use, i.e., pyocyanine (Schoental, R.: British Journal of Experimental Bacteriology, 22: 137, 1941).

Recently, penicillin, an extract of the fungus penicillus notatum, has been prepared by Chain, Florey, Gardner, Heatley, et al. (Lancet, 239: 226, 1940). This is non-toxic to living tissues while it is bactericidal and bacteriostatic in very high dilutions. A report of the clinical use of this compound by Florey et al. (Lancet, 241: 177, 1941) seems to show great promise.

Gramicidin has recently been prepared by Rene J. Dubos in the form of an extract from cultures of bacillus brevis. The original extract prepared was known as tyrothricin and has been found to consist of two compounds, tyrocidine and gramicidin. Tyrocidine is a general protoplasmic poison which is inhibited

by tissue extracts. Gramicidin is relatively non-toxic to animal and human tissues when applied locally but will selectively kill Gram-positive organisms such as pneumococcus, Streptococcus hemolyticus B, anaerobic Streptococcus, and Staphylococcus albus and aureus. It has only slight effect upon meningococcus and gonococcus. Tubercle bacilli are not affected. (Dubos, R. J.: Harvey Lecture, series 35, 223, 1939–40).

Gramicidin can only be used by local application as it is inactive and toxic when injected intravenously. It produces hemolysis of the red blood cells. Clinical investigations are in progress using tyrothricin and gramicidin solutions locally in the treatment of empyema, sinusitis, mastoiditis, Streptococcus hemolyticus and diphtheria carriers, and superficial ulcerations. The reports thus far seem to be favorable (personal communication from Dr. R. J. Dubos). Further application in the treatment of localized infections elicited by susceptible microorganisms seems warranted.

*The Story of The Mount Sinai Hospital, of which the first five installments appeared in preceding numbers of the Journal, is offered in celebration of the Hospital's ninetieth birthday. In its present form it consists mainly of brief historical notations which to some extent reflect the "way" of medicine in New York and elsewhere, as well as the changing environment since 1852. It has been compiled by Miss Jane Benedict from Hospital records, correspondence, medical and historical literature, and interviews with those who have been both eye-witnesses of and contributors to the Hospital's progress. It is presented mainly as source material from which later a more complete history of the Hospital is to be written.**

The preceding installments have carried the story of the Hospital from the founding of the old Jews' Hospital on Twenty-eighth Street, through the early years during which the institution gradually outgrew its first quarters and changed its name, to the planning of a new building at Lexington Avenue and Sixty-sixth Street. A description of the founders and the men of medicine and surgery who shaped Mount Sinai's tradition was accompanied by a brief account of contemporary practices in medicine, surgery, medical education, and nursing. Mount Sinai's participation in such crises as the Boyne Day riots, the cholera epidemic, and the Civil War was noted and its steady growth in medical resources and in capacity to serve was traced.

GROWTH AND DEVELOPMENT, 1870–1904

VI

On an afternoon in May of 1870, the Mayor of New York and the Directors of The Mount Sinai Hospital mounted the steps of a wooden platform erected above the dirt roadway at Lexington Avenue and Sixty-sixth Street. To the strains of Meyerbeer's *Marche aux Flambeaux*, they took their places for the ceremony of laying the cornerstone of the Hospital's new building.

In the presence of an enthusiastic gathering which included ". . . many prominent clergymen and citizens and quite a number of ladies (who) added the welcome charm of their presence,"[1] Mayor Oakey Hall set the stone in place and applied the mortar with an ivory-handled silver trowel. Speeches, ". . . frequently interrupted by hearty plaudits from the listeners,"[2] were made by Benjamin Nathan, the Hospital's President, and Emanuel B. Hart, its Vice-President, who placed in the cornerstone various newspapers of the day, several hospital reports, and some currency. Rev. J. J. Lyons, an old friend of Mount Sinai, offered a prayer, a service he had also performed when the cornerstone of

* Corrections, if errors of fact or interpretation are discovered, and additional information which may help to make the picture more complete are welcome and may be addressed to the Historian of the Hospital.

[1] The Jewish Messenger, May 27, 1870.

[2] New York Herald, May 26, 1870.

the first hospital building was laid in 1853. Eben's Band, a popular band of the day, played more music while the crowd dispersed to various carriages and drove off down the dusty road that was Lexington Avenue.

It was fifteen years since the modest four-story building on Twenty-eighth Street, Mount Sinai's first home, had opened its doors. During those years the Hospital had taken a position in the front rank of the city's philanthropies as a non-sectarian institution with a prominent medical staff. Its activities had so increased that the new building which the Directors and Staff were planning was to offer a 120 bed capacity in contrast with the 65 then available in the Twenty-eighth Street building. This great step in the expansion of facilities was an expression of the policy which has characterized Mount Sinai ever since—a constant desire to improve its service to the community, a persistent effort to satisfy the needs of the sick poor.

The drive for funds to erect the new building was initiated under the guidance of Benjamin Nathan, a kindly and generous figure in New York philanthropy. President of the Hospital since 1856, Benjamin Nathan had made a gift of ten thousand dollars to the institution in 1863, as had Joseph Fatman, also a member of the Board of Directors. The twenty-thousand-dollar donation was given with the understanding that it should form the basis for a permanent endowment fund and that the names of the donors should not be announced until after their death.[3] The generosity of Benjamin Nathan was known to his Board, however, and his leadership in the drive to erect the Lexington Avenue building was an inspiration to his fellow members. A few months before the laying of the cornerstone the Board was able to announce that sixty-five thousand dollars had been collected in subscriptions. In the midst of this fund-raising activity the Hospital was shocked by the sudden death of its President who was mysteriously murdered during a thunderstorm in the summer of 1870.[4]

The drive to erect the new building continued under the guidance of Emanuel B. Hart who succeeded Benjamin Nathan as President. On November 30, 1870, the Hebrew Orphan Asylum and Mount Sinai held "The Great Hebrew Charity Fair." The bazaars and booths remained open for three weeks at the Twenty-second Regiment Armory on Fourteenth Street. Thousands of visitors came and heeded the behest of the blue and gold lettering over the buffet: "Eat your food with pleasure; try to support your brother and the needy; and God will bless your work."[5] From this highly successful Fair Mount Sinai received approximately $101,675 to swell its fund.

It was at the Fair that Lazarus Morgenthau, a member of the Hospital Society, presented to the Directors a large leather-bound volume known as "The Golden Book of Life" in which were inscribed the names of those visitors and friends who contributed to the erection of the Lexington Avenue building. Intact to

[3] Minutes of Board of Directors' Meetings, The Jews' Hospital, October 4, 1863; November 8, 1863.

[4] Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, July 31, 1870.

[5] A Graphic Report from Federation for the Support of Jewish Philanthropic Societies, Vol. 1, No. 3, September, 1935.

this day, with its intricate design minutely wrought in pen-and-ink on the title page, the volume is a reminder of an earlier period which admired ornate scroll-work and elaborate decoration. Through the Golden Book of Life the Hospital collected $3,303.50.

By January of 1872, through the sale of the old Hospital and the receipt of various legacies, the Board announced that the building fund had been consider-

Benjamin Nathan
Hon. Secretary, 1852–1853
Vice-President, 1855–1856
President, 1856–1870

ably increased. There remained, nevertheless, a deficit of sixty-five thousand dollars before the total cost of three hundred and thirty-five thousand dollars could be attained. Fund raising, therefore, had to be continued after removal to the Hospital's Lexington Avenue home. (In 1904 $2,752,000 was to be raised for erecting on Mount Sinai's present site the ten buildings—many of them now altered or replaced—which formed the nucleus of the modern Hospital. Com-

pared with such a sum, $335,000 seems modest enough, but in the seventies it was a considerable amount to raise.)

The dedication of the completed building, which extended from Sixty-sixth to Sixty-seventh Street on the east side of Lexington Avenue, was held on May 29, 1872, in the garden at the rear. The Board had seen to it that ". . . a good band of music be in attendance and a choir of voices."[6] It had directed that "the yard be planked and an awning and seats erected and a platform arranged for the speakers and invited guests."[6] The opening prayer was offered by Rev. S. M. Isaacs, one of the founders of the Hospital. He had been a member of the Board of Directors until 1857, and had continued to serve Mount Sinai as one of the committee of ministers who regularly visited the patients. The inaugural address was made by the President, Emanuel B. Hart, who was followed by Governor John T. Hoffman.

The new home of the Hospital, described in a comtemporary publication as being "in the most approved style of architecture,"[7] was typical of public buildings of that period. Built of the "best Philadelphia brick" and trimmed with marble, it stood three stories high aside from the basement and attic.[8] The center portion was an administrative building which came to be known as the Middle House.[9] This was flanked on either side by passage-ways one story high which led to the wings. These extended farther back toward Third Avenue. Behind this central portion was a garden for the use of convalescents, and several small buildings containing machinery and apparatus.

The wings of the Hospital consisted of wards, the south for male patients and the north for female patients. The ground floor of the Middle House contained a reception ward which because of its size later came to be known as the "accident closet,"[9] a meeting room for the Board of Directors, and living quarters for the House Physician and Surgeon.[8] In later years this became the House Staff living room and a meeting place for the Attending Staff.[9] On the second floor were accommodations for private patients[8] and in years to come for the House Staff.[9] On the third floor were the operating rooms and a synagogue. Elevators, dumb-waiters, and steam heat were features especially emphasized by the press. The corridor floors were of marble, and heavy decoration, the style of the day, prevailed. Particular mention was made of ". . . columns, pilasters, pedestals and urns for containing flowers."[8] The architect was Griffeth Thomas who had designed ". . . the magnificent offices of the Park Bank, and other celebrated buildings about the city."[2] The *Daily Times*, in describing the plan, makes much of the spread between the wings: "The great feature of this building, which will certainly be one of the handsomest and most imposing in the city, is the distance—125 feet—between the pavilions. The greatest width yet given has not exceeded 110 feet. This is a most important point in establishments of this class, where light and ventilation are essential elements."[8]

[6] Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, April 20, 1872.
[7] Richmond, John Fletcher: New York and Its Institutions, 1871.
[8] Daily Times, May 15, 1870.
[9] Notes dictated by Dr. Percy Fridenberg, February 19, 1938.

With its red brick walls generously trimmed with white marble and its blue window shades,[10] The Mount Sinai Hospital on Lexington Avenue was one of the early landmarks in a comparatively uncrowded neighborhood. In 1872 the district between Sixtieth and Eightieth Streets was about as far "uptown" as the original Twenty-eighth Street building had been in 1855. New York's great period of expansion was well under way.[11] The removal of Mount Sinai to its Lexington Avenue site was an early part of the trend of public buildings and charitable institutions to uptown New York.

Although Mount Sinai, in 1872, dominated the immediate scene and commanded "a fine view of the Park and vicinity"[1] (Central Park was three blocks to the west!) there were other institutions which had likewise moved to that part

The Mount Sinai Hospital on Sixty-seventh Street. X shows the location of the Pathological Laboratory.

of the city. Farther downtown the Orphan Home and Asylum of the Protestant Episcopal Church had erected a building at Lexington Avenue and Forty-ninth Street. The Woman's Hospital founded by James Marion Sims, extended from Forty-ninth to Fiftieth Street. Nearby at Fifty-first Street and Lexington Avenue, stood the Nursery and Child's Hospital. The Presbyterian Hospital, founded four years before, had built farther uptown than Mount Sinai —from Seventieth to Seventy-first Street and from Madison to Fourth (Park) Avenue. The Presbyterian Home for Aged Women was at Seventy-third Street east of Madison Avenue, and the German (Lenox Hill) Hospital at its present

[10] Lilienthal, Howard: The Mount Sinai Hospital and Its Surgeons of the Middle Eighties: A Few Recollections, J. Mt. Sinai Hospital, Vol. III, No. 5, 1937.

[11] Wilson, James Grant: Memorial History of the City of New York, Vol. III, New York History Co., 1893.

site, Fourth (Park) Avenue between Seventy-Sixth and Seventy-Seventh Streets. One block east of the German Hospital, on Third Avenue, was the Hebrew Orphan Asylum which had benefited jointly with Mount Sinai at the Fair two years before.[12]

Open lots covered with squatters' shanties, like the one on Lexington Avenue opposite the Hospital, were not the only marks of a young New York in 1872.[13] Lexington Avenue and the side streets were all unpaved and in bad weather presented a sea of mud to doctors who drove hurriedly up in their buggies or carriages.[14] In 1871 the elevated railroad that ran up Ninth Avenue to Thirtieth Street failed, and from then until 1875 horse-cars and carriages were the only means of transportation in the city.[11] To get from one end of the constantly growing town to the other was a perplexing problem. In 1874, before the completion of the Brooklyn Bridge, a trip from Brooklyn to the German (Lenox Hill) Hospital followed this leisurely pattern: "To reach the Hospital from Brooklyn, I had to travel by horse-car to the Roosevelt Street ferry, cross the East River, walk up to Chatham Square and then board a Third Avenue horse-car which took me to Seventy-seventh Street."[15] Showing remarkable restraint, the author adds, "It was a tedious trip." With parts of the city still unpaved, street illumination only by gas, and the best transportation dependent on horse-power, New York in 1872 was still far from the days of rapid transit.

It was not long after Mount Sinai moved to its Lexington Avenue home, however, that signs of the city's steady growth began to appear. In 1873, the year following the Hospital's dedication, Hunter College, then known as the Normal College, erected its building at Sixty-eighth Street facing Fourth (Park) Avenue, thus becoming a close neighbor of Mount Sinai.[16] In the same year the New York Foundling Hospital moved to Sixty-eighth Street between Lexington and Third Avenues.[17] Lexington Avenue was paved in 1875.[18] Three years later the squatters' shanties on the west side of it disappeared[19] to be replaced by the Seventh Regiment Armory which moved uptown from Third Avenue and Sixth Street to its present site.[12] This presented its own problems in the form of shrilling bugles, tramping feet, and thumping drums. The minutes of the Board of Directors' meetings show great concern over ". . . a festival contemplated to be held in the Seventh Regiment Armory opposite this Hospital" because of ". . . the probable disturbance of the comfort of our inmates."[20]

Poor means of communication and transportation determined the speed with

[12] Valentine's Manual of the City of New York, 1875.

[13] Meyer, Alfred: Recollections of Old Mount Sinai Days, J. Mt. Sinai Hosp. Vol. III, No. 6, 1937.

[14] From photograph of Lexington Avenue building in its early days.

[15] Gerster, Arpad G.: Recollections of A New York Surgeon, Paul Hoeber, 1917.

[16] Information from Hunter College.

[17] Information from New York Foundling Hospital.

[18] Information from Department of Highways, New York City.

[19] Information from the Seventh Regiment.

[20] Minutes of the Board of Directors' Meetings, The Mount Sinai Hospital, September 12, 1880.

which doctors could be reached in the seventies and early eighties. If a member of the Attending Staff were needed at the Hospital—or, indeed, anywhere—there was nothing to do but go and fetch him. There were no telephones for emergency calls. Once transmitted to another part of the city, telegrams could only be delivered by hand and therefore were hardly quicker than a regular messenger. All that could be done was to dispatch an errand boy to the doctor's office and hope that he was not out in his buggy making calls. Until 1878 such a messenger had his choice of taking a hansom cab or the horse-drawn Third Avenue Railroad which stopped at Sixty-sixth Street just behind the Hospital.[12]

Four years after Mount Sinai moved to Lexington Avenue, Alexander Graham Bell invented the telephone. It was demonstrated at the Centennial Exposition in Philadelphia in 1876, but was considered simply a novelty. Slowly, however, its usefulness became apparent and a few instruments were installed. The year following the exposition, it was proudly noted that there were two hundred telephones in use "all over the United States."[21] By 1882 it was possible to call Mount Sinai on its newly installed telephone by asking for "Thirty-ninth Street, 257."[22]

The problem of transportation other than horse-power was finally tackled in 1875, with the passage of the Husted Act. This provided for a Commission to study rapid transit (or the lack of it) and make a recommendation to the city. One of the group appointed was Joseph Seligman who had been a member of the Hospital Board of Directors until 1862. The decision of the Commission was that ". . . elevated railways are not only more likely than any other to be actually constructed in this city, but are the best for the purpose in view."

In December of that year, 1875, building of such "railroads" began on Ninth, Sixth, Third, and Second Avenues. The following year the New York Company brought its lines up as far as Fifty-ninth Street and proudly announced that it was running "forty through trains each day." In 1878 the Sixth Avenue line ran from Rector Street to Central Park.[11] In the same year the Third Avenue line reached Sixty-sixth Street and erected a station on Third Avenue behind the Hospital.[23] In 1880 the Second Avenue line reached Sixty-seventh Street, and the same year two roads extended to Harlem.[11]

A comtemporary account describes public reaction: "The latest Herculean undertaking of New York has been the erection of elevated railways through the streets. The project had been in agitation a full dozen years before its successful issue in 1878, and neither the Erie Canal nor the Croton Aqueduct encountered more fierce and determined opposition. Horse-railroad companies and property owners brought suits and laid injunctions at every step. Charters were declared unconstitutional, and cases carried from tribunal to tribunal. When the battle was at last won, the helpless and hopeless community cried out in agony that the noise would kill business, the unsightly objects destroy the

[21] Leslie's History of Greater New York, Daniel Van Pelt, Arkell Pub. Co., 1898.
[22] Information from New York Telephone Co.
[23] Information from the Interborough Rapid Transit Co.

beauty of the city, and the moving trains in the air frighten horses and endanger human life. . . The noise quickly blended in the general din, the new sense of convenience displaced that of deformity, and the brute creation mildly observed and passed on, as if beyond surprise at any modern improvement in the city of New York."[24]

(To be continued)

[24] Lamb, Martha J.: History of the City of New York, A. S. Barnes & Co., 1879.

BILIRUBIN AND BILE SALTS IN JAUNDICE*

REUBEN OTTENBERG, M.D.

I. BILIRUBIN

1. Chemistry: Bilirubin is an intensely colored substance responsible for the staining of the tissues in jaundice. It is a good example of the power of advertising, for it is in itself an unimportant substance, useless, harmless, inert, devoid of any striking physiologic or pharmacologic effects. If it were colorless it would hardly be noticed; but its color has given it a conspicuous place in clinical medicine.

Bilirubin is pure excretion, a waste product which the body can no longer use, destined in the ordinary course of events—after bacterial decomposition to stercobilin (urobilin)—to be excreted as the coloring matter of the feces. It is only its occasional failure to be gotten rid of that makes it important. Its only value is nuisance value.

In human bile bilirubin is the essential coloring matter. On standing in the air the golden-reddish bilirubin of bile slowly undergoes spontaneous oxidation to the brilliantly phosporescent, green, *biliverdin.* The oxidation seems to be irreversible. In the bile of certain of the lower animals, as the dog, biliverdin is the predominating pigment. The proportion of the two varies from species to species depending on the state of oxidation of the bile. In the blood only bilirubin is found.

In recent years the chemical structure of bilirubin and related substances has been unravelled by the researches of Fischer, Willstatter and others. Interesting and unexpected relationships have been revealed.

There is an almost universal respiratory pigment known as heme some form of which is common to almost all living cells. Analysis has shown that it is composed of a circle of four pyrrol rings (Chart 1).

The pyrrol ring well deserves attention for it is turning out to be one of the widespread fundamental building stones of nature. It is five cornered, composed of four carbon atoms and one nitrogen. There is recent evidence that the animal organism can make its own pyrrol rings out of simpler substances (Whipple).

A circle of four pyrrol rings with side chains constitutes a *porphyrin.* Bilirubin is exactly like a porphyrin but the ring is open so that the four pyrrol rings are in linear arrangement.

Some porphyrins play a special role in pathology. Porphyrins have no respiratory properties; but remarkably enough the addition of a single metal atom at the center (connected with some of the nitrogen atoms of the pyrrols according to Fischer) endows the porphyrin molecule with remarkable respiratory properties, elevating it to the class of hemins (when the added atom is iron). In some of the lower animals the metal atom of the respiratory pigments is copper, and

*Lecture delivered in the Blumenthal Auditorium of The Mount Sinai Hospital, April 21, 1942.

in the plant pigment, chlorophyl, it is magnesium; but the general molecular structure is the same.

Hemins have to be carried by a protein (like most ferments) in order to exert their oxidizing powers. A glance at a famous diagram of McNee, which I have modified by placing it in parallel with a similar one of Anson and Mirsky (for heme in general) will give a clear idea of the place of bilirubin in the breakdown of hemoglobin. When hemoglobin breaks down (as it does every day in small amounts, and in every disease involving hemolysis in large amounts) the iron moiety (only 0.3 per cent) is scrupulously saved and stored away (in the form of hemosiderin) to be used over again by the body. It is suspected that

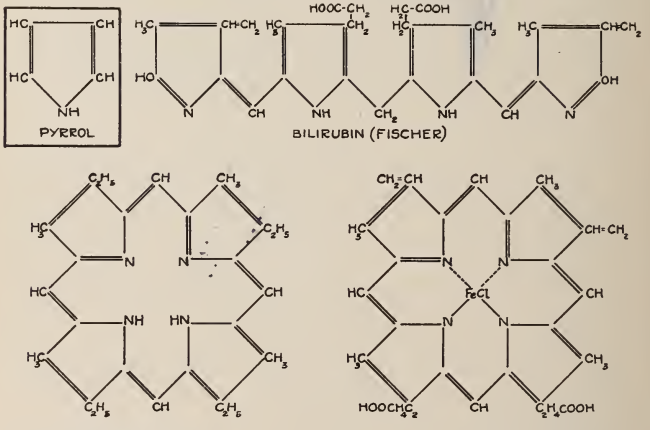


Chart 1. Relations of bilirubin, hemin and chlorophyl

the globin (which constitutes the great bulk, 95 per cent of the hemoglobin molecule) is also saved. But for some unknown reason bilirubin, or at least most of it, has to be excreted instead of being reconstructed.

In reviewing the properties of bilirubin the striking facts are its difficult water solubility, its easy solution in the presence of serum proteins (with which it enters into a loose combination) and its absence of physiologic or pharmacologic effects.

2. Detection and Measurement of Bilirubin in Blood: It was only in 1903 that Gilbert, using crude methods no longer employed, proved that small amounts of bilirubin are normal in the plasma of man (though not in that of certain lower

animals). Since the work of van den Bergh and Snapper in 1913 the measurement of blood bilirubin has become an important clinical procedure.

The old method, oxidation of bilirubin to biliverdin by the Gmelin reaction, has been dropped; and there are two general principles now in use, the icterus index and the van den Bergh methods.

A. The icterus index, introduced by Meulengracht in 1920 (and named by Bernheim and Stetten) is nothing but a direct comparison of the color of the serum or plasma with that of a standard 1:10,000 potassium bichromate solution. Thus if it is only necessary to dilute 5 to 15 times to match the standard the icterus index is 5 to 15 (this is the normal range).

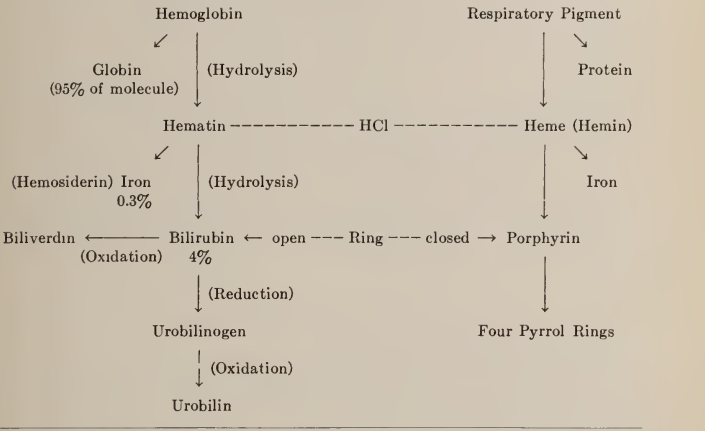


Chart 2. The diagram of McNee for the breakdown of hemoglobin and the diagram of Anson and Mirsky for the breakdown of respiratory pigment, arranged in parallel

Although it is not a chemical test but merely a color comparison the icterus index is valuable and fairly accurate. The other pigments (carotin, lutein) of serum seldom occur in more than traces. The chief difficulty is due to traces of hemoglobin in the serum resulting from technical imperfection in its collection.

For this reason a modification of the icterus index has been introduced (by Ernst and Forster) in which hemoglobin and other proteins are precipitated out by an excess of acetone before the color comparison is made.

Unfortunately the acetone precipitates not only the hemoglobin present but also a large and variable amount of the bilirubin. For this reason the readings differ widely from those of the original (now called the "*water*" method); usually they are $\frac{1}{2}$ to $\frac{1}{3}$ as much. Normals give an index of 3 to 6 instead of 5 to 15. It happens that the bilirubin precipitated by the acetone is exclusively of the peculiar type common to obstructive jaundice and liver necrosis and known as

"direct reaction." Hence, Reiner and Weiner pointed out, if one determines both the original water icterus index and the acetone index and there is no difference one can diagnose a hemolytic type of jaundice. For the same reason the acetone modification is extremely accurate for small amounts of bilirubin (which are usually "indirect reacting") but extremely inaccurate for large amounts (which are largely "direct") (Newburger).

Some hospitals report on the original, some on the acetone modification. Our laboratory uses the acetone method as routine (giving the original also when specially requested). My preference is for the original method because it is so simple that any practitioner can do it. Only one must take real care that no hemolysis occurs in collecting the blood; this is readily accomplished if one takes $\frac{1}{10}$ volume of isotonic ($2\frac{1}{2}$ or 3 per cent) sodium citrate in his syringe and does the estimation on plasma instead of serum.

B. The van den Bergh test is an almost specific color reaction for bilirubin. Ehrlich discovered as early as 1883 that a fresh mixture of sulfanilic acid and sodium nitrite would give a beautiful purple color with bilirubin. The reagent is known as Ehrlich's diazo reagent. Its specificity was shown by Proscher in 1900 but it was not until 1913 that van den Bergh and Snapper used it for deter-

Crystallizable. Soluble in chloroform. Soluble in strong alkali (pH 8-12). Soluble in serum (its best solvent).
Insoluble in water. Insoluble in saline solution. Insoluble in cerebrospinal fluid.
Slightly soluble in lymph. Practically no physiological or pharmacological effects. Non-toxic.

CHART 3. Some properties of bilirubin

mination of blood bilirubin and discovered the peculiar significance of the so-called "direct" and "indirect" reactions.

In the direct method the color appears at once or in a few moments when the reagent is added to serum. The direct reaction is obtained only in liver diseases and obstructions of the bile ducts.

In the indirect method the reagent is added to serum from which the proteins have been precipitated by an excess of alcohol. The indirect reaction is given by the small amount (1 mg. per 100 cc. or less) of bilirubin in normal serum and by the serum of all the very numerous forms of hemolytic jaundice.

Since normal serum gives an indirect reaction every serum that gives a direct reaction will also give an indirect one to at least some degree (but not the reverse).

The terms "prompt" and "delayed" are often used in reporting the van den Bergh reaction. Also the term "biphasic" is often used for serum which has a considerable amount of indirect as well as some direct reacting bilirubin. These terms should be dropped as their meaning is uncertain and they have no diagnostic significance. Only the terms "direct" and "indirect" should be used as the difference between them is unmistakable and has deep biologic meaning.

The differences between direct and indirect van den Bergh reactions are not merely quantitative but qualitative and have turned out to be of great clinical important (Chart 4).

Time does not permit me to do more than point out the many differences (Chart 4). The most significant facts are that indirect reacting bilirubin is characteristic of normal human blood and of hemolytic diseases, that the direct is the variety found in bile and excreted in urine (in man).

The exact nature of the difference between the two, and the explanation for the peculiar differences in behavior which I have tabulated are not yet clearly understood.

It was first supposed that indirect bilirubin was bound to some serum protein while direct was free. But recent studies by cataphoresis, ultracentrifuge and ultrafiltration have shown that both kinds are bound to serum albumin though the indirect is probably more firmly bound (Coolidge).

When pure crystallized bilirubin (which gives the direct reaction) is injected into the blood stream, as in the bilirubin load test, or added to serum in small amounts, it gives only the indirect reaction. But this is relative (Barron) as larger amounts added give the direct reaction.

Direct reacting bilirubin (Cholebilirubin)	*Indirect* reacting bilirubin (Hemobilirubin)
1. Excreted in urine	1. Not excreted (in man)
2. Precipitated with proteins (alcohol, acetone)	2. Not so precipitated
3. Oxidized to biliverdin	3. Not readily oxidized
4. Stains renal epithelium	4. Does not stain renal epithelium
5. Found in bile	5. Not found in bile
6. Poorly soluble in chloroform	6. Readily soluble in chloroform
7. Does not stain the brain	7. Stains some nerve centers ("Kern icterus")
8. Does not crystallize post-mortem	8. Crystallizes post-mortem in tissues

CHART 4. Differences in behavior between direct and indirect reacting bilirubin

This has led some to claim that the difference between the two was merely a matter of quantity, but this is certainly not correct. The blood of some hemolytic diseases and of the newborn may contain as high as 28 mg. per cent with only the indirect reaction; while the addition of the minutest trace (2 mg.) of gall bladder bile to serum gives the direct reaction.

The difference between the two is in some way related to bile salts since addition of bile salts to indirect reacting serum changes it to direct (Barron), and most of the diseases which give direct reaction have bile salts in the blood while none of the diseases which give indirect reaction have.

How the bile salts work is not certain. Foweather believes there is a real chemical difference, indirect reacting bilirubin being a keto, direct an enol form. Sobotka and Kahn have shown that bile salts alter the balance between keto and enol forms of certain ketones, producing stable enol forms, and it has been suggested that this may be the chemical mechanism (Chart 5).

On account of the extremely variable loss of bilirubin by alcohol precipitation, the quantitative van den Bergh test has always been unreliable, being in reality little more accurate than the much simpler icterus index. Using the photoelectric colorimeter Malloy and Evelyn have introduced a far more precise

quantitative method. Van den Bergh had assumed that indirect bilirubin would only couple with diazonium salt after precipitation of the proteins of serum by alcohol. Malloy and Evelyn, however, found that precipitation was not necessary and complete coupling was obtained in 50 per cent methyl alcohol without precipitation of proteins. By this method direct as well as indirect reacting bilirubin can be measured exactly in all varieties of jaundice.

Our current conceptions of blood bilirubin have been acquired largely by the method of van den Bergh or one of its modifications; this new method, which has not yet received extensive clinical application, may lead us to alter many of them.

3. In what tissues is bilirubin produced? Until twenty-five years ago everyone accepted what looked like the obvious answer, that bilirubin was formed by the cells of the liver. This was apparently supported by the well known experiments of Minkowski and Naunyn in 1886 in which hepatectomized geese failed to develop jaundice in spite of intravascular hemolysis.

There had been, however, a few straws pointing in the opposite direction. Virchow recognized that hematoidin, produced from hemoglobin in blood extravasations was closely related to bilirubin. Löwit (1889) suggested on

Many compounds change in presence of bile salts from a

Keto form to a tautomeric *Enol* form

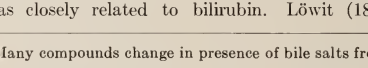


CHART 5. Explanation suggested (Sobotka) for the change from indirect to direct reacting bilirubin

histologic grounds that the Kupffer (stellate) cells of the liver sinusoids might form bilirubin. McNee (1914) repeated the Minkowski-Naunyn experiments but explained them differently as due to removal by hepatectomy of the very large amount of reticulo-endothelium (Kupffer cells) present in the liver of the goose.

Whipple and Hooper in 1913 opened the new era by showing that a liverless dog continues to pour bilirubin into its blood stream and indeed (in spite of their shock producing procedure) as large an amount as one-fifth of the normal daily quantity.

The dispute was settled, however, in 1925 by Mann and his co-workers at the Mayo Clinic in their famous hepatectomy experiments in dogs. By examining the bilirubin content of the blood coming from various organs they were able to trace conversion of hemoglobin to bilirubin directly to the reticulo-endothelial tissue represented by bone marrow, spleen, lymph nodes, and Kupffer cells. The largest amounts were formed in the marrow.

The function of parenchymal liver cells then is not to form bilirubin but to absorb it from the blood stream and to excrete it. The bile stain of metastases from primary liver carcinoma (which had previously been regarded as proof of

their manufacture of bilirubin) is really due to their great power of absorbing it from the blood.

The bilirubin poured into the blood stream by the reticulo-endothelial tissues only gives the indirect van den Bergh reaction. At the same time Rich (1925), in tissue culture experiments, showed that hematoidin is bilirubin, that it is only formed intracellularly and only in cells of mesodermal origin. His efforts to detect a formative enzyme were negative.

4. Quantitative Studies of Bilirubin Formation: Whipple and his associates, in an extraordinary series of experiments from 1914 onward, proved that hemoglobin and its analogue in the muscles, myoglobin are the only source of bilirubin. But they showed that not all the hemoglobin derived from laked red blood cells is necessarily converted. Depending on the state of anemia, i.e., the state of need of the animal, a variable proportion of hemoglobin (even from another species of animal), is retained and built up into red blood cells.

Until 1915 supposed to be formed by liver cells.
Although: Virchow recognized hematoidin was related to bilirubin (1847). Löwitt (1889) showed Kupffer cells form bilirubin. McNee (1914) confirmed this experimentally.
1916, Whipple and Hooper: Liverless dog forms bilirubin.
1925, Mann and co-workers: Bilirubin formed in reticulo-endothelial cells of marrow, spleen, lymph nodes and Kupffer cells, but not in liver cells.
1925, Rich: Hematoidin is bilirubin and is formed in tissue cells.

Chart 6. Location of bilirubin formation

This was confirmed by the work of Rous, McMaster and others who showed that the amount of bilirubin formed after injection of hemoglobin is always smaller than one might expect from chemical calculations.

The extraordinary quantitative studies of the Whipple group on the amounts of bile pigment and of hemoglobin produced under varying conditions in dogs whose entire bile was collected by side-tracking it into the pelvis of the kidney also seem to prove beyond a doubt that the dog's body can construct the pyrrol nucleus.

Under normal conditions the amount of bilirubin produced per day is rather small and fairly constant about a half gram for human beings and at about the same rate, 5 to 8 mg. per kilo, for most experimental animals. It is diminished in anemias and increased in every form of hemolytic disease. The amount in human disease can be estimated from the total of the degradation product, urobilin, in stools and urine.

What happens to the excess bilirubin in prolonged obstructive jaundice when most of the bilirubin cannot escape from the body is a mystery. In these cases the blood bilirubin, instead of increasing progressively with every daily accretion of bilirubin, as perhaps would be expected, soon reaches a moderately high plateau and remains there. Only a small part of the amount formed daily is accounted for by urinary excretion and deposit in the tissues and intestinal excretion (of which traces are found after a month or more). Either the hemoglobin of worn out red blood cells must be disposed of by some other mechanism, or the body must have some way of destroying the excess of bilirubin.

5. Excretion of Bilirubin: All bilirubin formed in the body is normally excreted by the liver cells, and injected bilirubin can be recovered almost quantitatively in the bile.

Even in the dog, which has no renal threshold for bilirubin, the amount excreted in the urine is only a fraction of 1 per cent of that injected. In man injected bilirubin does not appear in the urine at all (but the amounts injected in man have always been comparatively small). There must be a difference in the speed or mechanism of removal of newly formed bilirubin from the plasma of dog and monkey on the one hand and of man on the other. For dog's serum is normally white and contains no or bare traces of bilirubin while man's serum is normally yellow and contains up to 1 mg. per cent (all indirect reacting). The difference is that dogs' kidneys allow indirect bilirubin to pass, human kidneys not at all (Aschoff).

Chart 7. Elimination of injected bilirubin from blood (Eilbot)

Direct reacting bilirubin, when it appears in the blood as the result of disease or experiment, is excreted by the kidneys. Van den Bergh claimed that there was a renal threshold of 1.4 to 1.8 mg. per cent but recent work indicates that any amount of direct reacting bilirubin is excreted without a threshold.

The duration of stay of bilirubin in the blood is dependent on the functional state of the liver only. Bergmann and Eilbot in 1927 took advantage of this and introduced the bilirubin load test. Small amounts (70 mg.) of purified bilirubin are injected intravenously and the amount remaining in the plasma after four hours is determined. Harrop and Barron and then Soffer did extensive work with this test and showed it to be the most delicate test of liver function (in the absence of jaundice). Soffer and Paulson showed it to be delicate enough to differentiate between normals and persons who had had simple jaundice a

year or more before. However, it is expensive and a good deal of trouble (requiring four venipunctures) and limited in application to non-jaundiced cases. Therefore it has not come into wide practical use.

6. Relation of Bilirubinemia to Jaundice: In jaundice bilirubin first appears in the blood then stains the tissue lymph and finally the cells. With increasing or maintained jaundice the serum bilirubin is higher than that of the tissue lymph (cantharides blister) and at times the direct van den Bergh reaction is given by the serum, but only the indirect reaction by the lymph. In subsiding jaundice the lymph shows more than the blood.

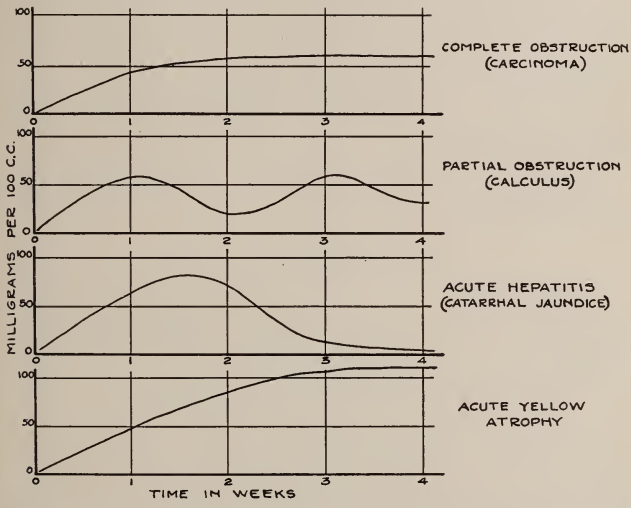


Chart 8. Typical blood bilirubin curves

The laws which control the diffusion of blood bilirubin into the tissues are not known, and there are many as yet unexplained facts. Thus, in jaundice the cerebrospinal fluid of adults is not stained (bilirubin is insoluble in cerebrospinal fluid) but that of infants sometimes is. The central nervous system does not stain (except "kern icterns" in infants) but the dura mater and peripheral nerves do. The pancreas and spleen are said to contain hardly any bilirubin while skin and serous membranes contain the largest amounts. It is stated that bilirubin is excreted in sweat and in milk (Klemperer) but I have never noticed it in sweat.

Jaundice appears within a few hours when due to indirect bilirubin (for example hemolysis from mismatched transfusion).

With regard to the quantity of bilirubin in the blood a single test is of little significance, but a series of tests giving a curve is of great value.

II. BILE SALTS

1. When we come to bile salts we are dealing with substances quite unlike bilirubin which is a mere excretion; we have here substances of immense power, peculiar activities, indeed indispensable to life. Except for its content of bile salts bile would be a mere excretion like urine; the real function of the secretion of bile is to put bile salts into the intestines. When bile salts fail to reach the intestine all animals sooner or later die with mysterious symptoms of hemorrhagic disease, anemia, cachexia, bone resorption. The existence of this clinical picture has been known for a century but its explanation has only come in recent years. It is due to failure of absorption of essential lipoids, vitamins, and calcium, all of which depend for their absorption on bile salts.

2. The mechanism of action of this remarkable group of substances is only incompletely understood. For brevity their principal properties may be enumerated as follows:

1. Intestinal absorption of (a) fats and fat soluble substances; (b) vitamins A, D, E, K; (c) calcium and magnesium. (Hence ultimately essential to life.) 2. Regulation of bile secretion—cholagog effect.

CHART 9. Physiological functions of bile salts

1. Powerfully lower surface tension, favoring emulsification of fats, dissolving lecithin and cholesterin. 2. Make numerous insoluble compounds water-soluble by coupling with desoxycholic acid (Wieland). 3. Penetrate cells (e.g., red blood cells). 4. Hemolytic effect inhibited by serum. 5. Lytic to pneumococci, trypanosomes and some other organisms. 6. Very soluble. Dextro-rotary. Colorless.

CHART 10. Bile salts—some physical properties

3. The chemical structure of bile salts has been unravelled in the last decade along with the structure of the vast and important group of steroids and steroid hormones.

The simple (or unconjugated) bile salts are all built on a structure almost identical with the peculiar four ring carbon frame of all the steroids. It differs only in the steric configuration of one carbon atom - # 5. To be noticed are the three OH groups and the terminal COOH which gives the acid properties, leading to the formation of the alkaline sodium salts actually excreted. Unconjugated bile salts only form a small amount, 10 to 20 per cent of the salts in bile, varying in proportion according to physiologic conditions and disease.

According to the side groups there are at least *seven naturally occurring* and a large number of synthetic bile salts.

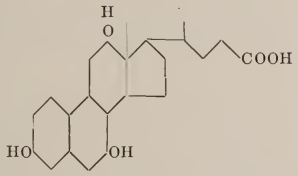
The bulk (80 to 90 per cent) of the bile salts are in conjugated form. All the bile salts conjugate in a peptid-like lineage with either glycine, to form glycocholic and or with taurin to form taurocholic acid. In quantity cholic acid is the predominant bile acid. Glycocholic and taurocholic acids are both present in man and in cattle; only taurocholic in the dog and many other species.

Despite the similar structure there is no evidence that bile acids are derived from steroids.

4. *Where are Bile Salts Formed?* It is nearly always assumed that bile salts are a specific product of the liver cell. Aschoff, however, points out that this assumption (similar to the one so many years mistakenly made for bilirubin) has not been absolutely proved. Many authors report that bile salts can be found in normal blood; and Mann and Magath reported that in some experiments liverless dogs which lived long enough showed a positive Pettenkofer reaction in their blood. This raises the important question:

5. *Are Bile Salts Present in Normal Blood?* Here authorities separate into two absolutely opposed schools. A large number (Aldrich, Bledsoe, Shattuck, Rowntree, Greene, Lichtman, and others) report anywhere from 3 to 12 mg. 100 cc. of blood. On the other hand a long series of chemists from Hoppe Seyler to Gregory, Pascoe and Jenke state that no bile salts can be detected in normal blood and that all the claims for their normal presence are based on uncritical

(1) Unconjugated bile acids. Seven or more occur naturally, $C_{24}H_{39}O_5$ (no N), cholic, desoxycholic. Only small amounts found in bile. All built on the same four ring carbon frame as the steroids:



(2) Conjugated. Any bile acid conjugated with an amino acid. Glycine (glycocol) to form glycocholic acid which predominates in bile of man (contains N). Taurin to form taurocholic acid which predominates in many other species (contains N and S).

Chart 11. Chemistry of bile salts

use of the Pettenkofer color reaction, whose extraordinary delicacy and specificity can only be relied upon if the red color is positively identified by a spectroscopic absorption band.

6. *The idea of* exclusive formation by liver cells is to some extent supported by the behavior of bile salts in experimental or clinical complete occlusion of the bile duct. The amount of bile salts in the blood becomes very high (up to 55 mg. per cent) at the start, but diminishes and finally disappears altogether. This is in contrast to blood bilirubin. If the liver only excreted bile salts formed elsewhere one could hardly explain the final disappearance from the blood.

On the other hand experiments with liver cell poisons and observations on clinical hepato-cellular disease are not so easily explained. The secretion of bile salts is extraordinarily sensitive to liver poisons. Thus, chloroform or carbon tetrachloride cause bile salts in bile to diminish greatly or even temporarily disappear (Smith, Whipple, Smyth). However, not too much stress should be laid on this because all sorts of intoxications and infections and even simple

operative procedures seem to depress bile salt secretion (Doubilet). On the other hand, in many cases of clinical liver necrosis bile salts in the blood are moderately increased (20 to 30 mg. per cent).

7. *Secretion and Internal Circulation of Bile Salts:* Whether the liver synthesizes bile salts or not it has great power of excreting bile salts. The liver of a dog will excrete within two hours as large an injected dose as 0.5 gram per kilo of body weight. The amount normally secreted by the human liver in twenty-four hours is large (compared for example with 0.5 gram of bilirubin) 10 to 20 grams.

However only a small fraction, $\frac{1}{7}$ to $\frac{1}{10}$, of this large amount is synthesized on that day. The remainder is simply resorbed from the intestine, along with the food whose absorption it has facilitated, carried in the portal blood stream back to the liver and re-excreted. Only a small fraction escapes in the feces.

8. The amount of bile salts synthesized can, however, be vastly increased. For example when a total biliary fistula is formed the liver at first keeps on secreting as much bile salt as before, i.e., about ten times as much as usual must be spontaneously formed. Gradually the amount formed lessens.

The quantity synthesized is greatly increased by feeding meat and certain amino acids such as tryptophane, proline, aspartic acid (Whipple and Smith). How these produce the effect is not clear since they are not the amino acids used for coupling with cholic acid, nor so far as known, are they directly used in formation of cholic acid.

9. The liver is not the only organ which can excrete bile salts. The kidneys excrete all the bile salts that reach them in the blood. After removal of the liver a dog's kidney, can excrete as large a dose injected as 3 grams in twelve hours (Bollman, Mann). The amount of bile salts excreted per day in the urine in permanent bile duct obstruction is only $\frac{1}{3}$ to $\frac{1}{2}$ that excreted in a biliary fistula.

10. Apparently the liver not only can form and excrete bile salts, but can destroy them as well. If bile salts are injected into an animal with obstructed bile duct, only a fraction is excreted in the urine. The liver is able to destroy one-half as much per day as it can synthesize. That the liver is responsible for this is evident because after hepatectomy the injected bile salts are excreted quantitatively in the urine.

11. The question of the toxicity of bile salts in the blood has been much debated. Bile salt injections (in much larger amounts, however, than ever reach the blood clinically) are acutely toxic. But all the old claims that bile salts are responsible for cholemia have been dropped. Clinicians believe them to be responsible for the itching of jaundice, and perhaps for the slow pulse.

12. *Therapeutic use:* The unique property of bile salts of stimulating the flow of bile has led to their use for this purpose in disease.

13. By mouth they are also given in obstructive jaundice and in bile fistula cases to aid absorption of fat and particularly of vitamin K. For intravenous use an artificial derivative of the bile salt, dihydrocholic acid, (Decholin) has been found practically non-toxic even in doses as high as 2 grams. This sub-

stance which has all the three OH groups oxidised to keto groups retains the bile secretion stimulating property but lacks the ability of bile salts to dissolve insoluble substance.

14. Although bile salts are substances of tremendous importance their determination in blood or urine is at present of little or no practical clinical value.

Josephson, however, has recently introduced a bile salts excretion test similar in principle to the bilirubin load test of Eilbot, a half gram of sodium cholate

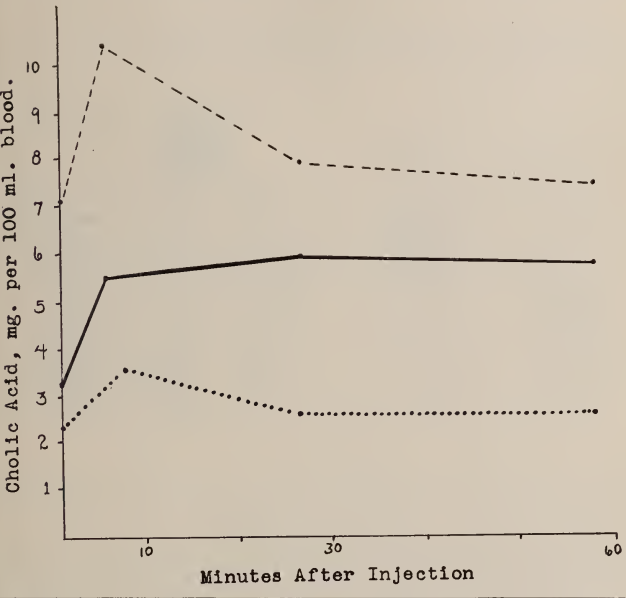


Chart 12. Bile salt load test (Josephson) typical curves

·--------· Obstructive Jaundice. ·———· Hepato-cellular Jaundice. ·.....· Normal.

is injected intravenously. Calculation will show that this should raise the bile salt level of the serum, if uniformly distributed, to over 20 mg. per cent but the removal of bile salts from the blood is so astoundingly rapid that in five minutes the blood level is only 5 or 6 mg. per cent (Chart 12).

In persons without jaundice and in obstructive jaundice the removal of the remainder of the injected bile salt is very rapid, so that at the end of one-half hour the blood level is nearly what it was before the injection (Chart 12).

In most cases of hepatitis, however, (7 out of 11) the removal is very slow so that at the end of one-half hour the blood level is only 1 or at most 2 mg. lower than at five minutes. The liver cells seem to have lost their power of absorbing cholate. This test, unlike the bilirubin load test which is applicable only to non-jaundiced liver disease, is of value only in the presence of jaundice. With simplification of technique, which is promised by the author, it may become a valuable diagnostic method.

III. JAUNDICE

Understanding of jaundice is much clarified by Rich's conception (1925) of division into retention jaundice and regurgitation jaundice.

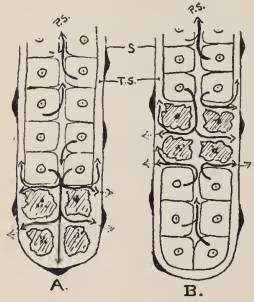


Fig. 1

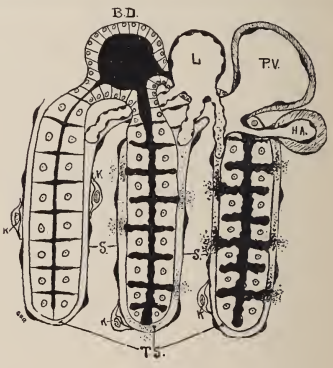


Fig. 2

Chart 13. Rich's Diagram—Mechanism of Regurgitation Jaundice in Liver Cell Necrosis and in Bile Duct Obstruction

Retention in the blood stream of bilirubin formed by the reticulo-endothelial system but not yet excreted through the liver cells, may be due to over production of bilirubin (as in every variety of hemolysis), or to functional impairment of liver excretion (as from anoxemia, circulatory disturbances or toxic liver cell damage short of necrosis). The serum shows only the indirect van den Bergh test no matter how intense the jaundice.

Regurgitation implies reentry into the blood stream of fully formed bile already excreted into the biliary canaliculi and, therefore, containing bile salts, cholesterol, etc. (Chart 13). Many observers have confirmed the observation (Haberland, 1925) that in obstructive jaundice bile pigment is carried to the blood largely via the thoracic duct, i.e., (referring to Rich's diagram) that it first enters the lymph of the tissue spaces and does not break directly through the blood capillary walls.

The interesting observation has been made (Barron and Bumstead, 1928; Mayo and Greene, 1929) that after tying of the common bile duct the first phenomenon is appearance of indirect bilirubin in the thoracic duct, and then one or two hours later in the blood. Only at four or five hours does direct bilirubin appear in the thoracic duct and then one or two hours later in the blood. This has been interpreted (Aschoff) by assuming that at first there is a reflex cessation of secretion by the liver cells so that indirect bilirubin brought to them is turned back to the lymph.

It is only when back pressure has become sufficient (refer to Rich's diagram) to force bile back between liver cells into lymph spaces, (or to rupture the ampullae of the interlobular bile ducts according to Heidenhein and Hiyeda) that bile (at four or five hours) gets into the lymph. Rich also postulates regurgitation directly into the blood stream.

In liver-cell necrosis the same regurgitation of bile through gaps between liver cells into tissue spaces explains the entry of direct reacting bilirubin into the blood.

We thus may elaborate Rich's classification of bilirubinemia (Chart 14).

I. Retention of bilirubin (characterized by indirect van den Bergh) and due to (a) overproduction (i.e. hemolysis), (b) functional impairment of liver.
II. Regurgitation of bile (characterized by direct van den Bergh) and due to (a) obstruction of ducts, (b) necrosis of liver cells.

Chart 14. Jaundice (Rich's classification)

Clinical considerations have gradually made it clear that in many instances of jaundice, not merely one of these mechanisms is involved, but two or even three or all four in varying degrees. This is what makes diagnosis difficult.

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EFFECT OF PROLONGED LECITHIN FEEDING ON HYPERCHOLESTEROLEMIA

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The significance of hypercholesterolemia is not well established. It may lead in some instances to severe organic changes, particularly in the cardio-vascular apparatus. Therapeutic attempts with diets, free of cholesterol and low in fats, were limited in success.

The interdependence of cholesterol and lecithin in many biological processes, and the lipotropic effect of lecithin and choline suggested therapeutic trials with lecithin in hypercholesterolemia. Lecithin has recently become commercially available in large amounts and at a price permitting prolonged clinical administration. Amounts from 10 to 70 grams of soy bean lecithin may be taken in palatable form (cookies) and produce but rarely, when given in excessive amounts, gastric discomfort in sensitive individuals. We have studied the effect of lecithin feeding on several blood constituents and on the intestinal adsorption of fat and vitamin A in man.[1] Whereas the cholesterol level of the serum in normals shows an ephemeral downward trend, prolonged feeding does not affect it.

In five cases of hypercholesterolemia, associated with various clinical conditions, a striking decrease of the serum cholesterol level was achieved by addition of commercial lecithin to the diet (see accompanying table).

The serum cholesterol decreased considerably in all cases, apparently as a result of the lecithin feeding. In Case 1, a cirrhosis of the liver and xanthomatosis, the total lipids of the serum dropped parallel to the cholesterol, and remarkable clinical improvement was observed. In Case 2, a generalized xanthomatosis, the decrease of the serum cholesterol followed the administration of lecithin, but was associated with no striking clinical changes. Six months after the feeding of lecithin was stopped, the serum cholesterol had returned to its former high level. In Case 3, a case of diabetes and obesity, the serum cholesterol dropped by about one-third during lecithin feeding, but was found back at the elevated level 7 months after the feeding of lecithin had been stopped. In Case 4, one of localized xanthomatosis, the feeding of lecithin caused a diminution of the total and particularly, of the esterified serum cholesterol. Simultaneously xanthelasmata of the lids diminished in thickness, but failed to disappear. A similar observation was made in Case 5, whose xanthomatosis was complicated by psoriasis.

Commercial soy bean lecithin represents a mixture of the following composition: lecithin, 20 per cent; cephalin, 20 per cent; soy bean oil, 30 per cent; carbohydrates, 10 per cent; inositol and allied compounds, 15 per cent; phytosterols, 2 per cent. The described effects[1] cannot be ascribed to soy bean oil,

[1] Adlersberg, D., and Sobotka, H.: Effect of lecithin feeding on fat and vitamin A absorption in man. To appear in J. Nutrition, Vol. 25, 1943.

since they could also be produced with defatted products. The role of cephalin and inositol remains to be studied.

TABLE I

Effect of lecithin feeding on serum cholesterol level

CASE	DATE	SERUM CHOLESTEROL (MG./100 CC.)
Case 1. Female, 38 years, biliary cirrhosis, cholangitis, pericholangitis, xanthomatosis. 15 grams defatted lecithin *per diem* during period indicated.	5/28/1941	1420
	7/28	1370 (Total lipoids 3850 mg./100 cc.)
	8/ 1	Lecithin started
	8/ 2	1050 (Total lipoids 3400 mg./100 cc.)
	8/11	Lecithin stopped
	8/15	740
	8/28	875
	8/28	Lecithin resumed
	9/ 2	770 (340)*
	9/10	630 (360) (Total lipoids 1575 mg./100 cc.)
	9/11	625 (330)
	9/15	540 (340)
	9/19	590 (340)
	11/ 3	445 (315)
Case 2. Female, 48 years, xanthomatosis of palms and lids. 15 grams soy bean lecithin *per diem*.	1/21/1942	875, Lecithin started
	2/12	550, Lecithin stopped
	4/ 6	530
	6/ 1	560, Lecithin resumed
	6/15	430
	7/16	295, Lecithin stopped
	1/12/1943	570 (400)
Case 3. Female, 55 years, diabetes, obesity. 15 grams soy bean lecithin *per diem*.	9/20/1941	360
	9/24	Lecithin started
	10/18	365
	11/ 8	235, Lecithin stopped
	6/27/1942	500
Case 4. Female, 41 years, xanthomatosis of lids and palms. 12 grams soy bean lecithin *per diem*.	11/10/1942	620 (550) Lecithin started
	12/ 8	460 (220)
	12/22	470 (330)
	1/ 5/1943	420 (270)
	2/ 9	300 (205) Lecithin continued
Case 5. Male, 35 years, xanthomatosis of lids, extensive psoriasis. 12 grams soy bean lecithin *per diem*.	11/14/1942	440 (345) Lecithin started
	1/12/1943	260 (180) Lecithin continued

* Esterified cholesterol values in parentheses.

Summary: Five cases of xanthomatosis and hypercholesterolemia showed a striking decrease of the serum cholesterol level upon prolonged feeding of lecithin. A few months after the feeding of lecithin was interrupted, the serum cholesterol returned to the original high figures. Further therapeutic trials are suggested.

ELECTROENCEPHALOGRAPHIC STUDIES: BILATERAL DIFFERENCES IN ALPHA ACTIVITY IN CASES WITH AND WITHOUT CEREBRAL PATHOLOGY

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It is generally assumed that in normal individuals the bilateral difference in electrical activity of homologous cerebral areas as recorded by the electroencephalogram is relatively small, although there is a tendency to a greater percentage of alpha activity on the non-dominant side. Lindsley (2) measured the periods of spontaneous disappearance (blocking) of alpha activity. He found that in right-handed subjects the mean per cent of blocking time on the left (1.3 per cent) was slightly greater than on the right (0.9 per cent). In the left-handed group he found that the blocking was slightly greater on the right (1.9 per cent) than on the left (1.7 per cent). Raney (3) found a more pronounced difference in identical twins with very definite sidedness. In some schizophrenics, Jasper, Fitzpatrick, and Solomon (1) found a pronounced bilateral difference in alpha activity recorded from homologous regions of the head without mentioning any relation to the dominant hemisphere. Several authors have pointed out incidentally, that a unilateral depression of alpha activity may be found in focal lesions (5). According to Shmelkin (4), such a depression may be the only electroencephalographic indication of a focal vascular lesion.

A bilateral difference in alpha activity can have diagnostic significance only if we possess exact knowledge about the corresponding facts in subjects without indication of a cerebral lesion. This paper is concerned in its first part with work providing these standard values. Its second part gives results of similar studies in patients with cerebral lesions.

METHOD

Technique: The records were taken with a three channel Grass electroencephalograph, in a shielded semi-dark room while the subjects were resting with the eyes closed. Eleven solder button electrodes (5 mm. in diameter) were used in each case: 2 symmetrical "frontal" electrodes (placed one-half the distance between the nasion and vertex and 3 cm. on either side of the midline), 2 symmetrical "central" electrodes (placed one-half the distance from the nasion to the inion and 3 cm. on either side of the midline), 2 symmetrical "parietal" electrodes (placed 4 cm. behind the vertex and 7 cm. on either side of the midline), 2 symmetrical "occipital" electrodes (placed 3 cm. above the inion and 3 cm. on either side of the midline), 2 so-called "indifferent" electrodes (placed on the right and left ear lobes), 1 "vertex" electrode (placed on the midline halfway between the nasion and the inion). Records with symmetrical leads were taken simultaneously from each of the four above-mentioned regions (frontal,

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central, parietal and occipital). Both the indifferent and the vertex leads were used successively. In addition, records were taken with fronto-central, centro-parietal and parieto-occipital leads. The duration of record from each lead was at least 1.5 minutes.

PART I

Subjects: Eighty-one patients at The Mount Sinai Hospital were used as subjects. None of these patients showed any clinical indication of diffuse or focal

TABLE 1

INDEX OF ASYMMETRY	PARIETO-INDIFFERENT LEADS			PARIETO-VERTEX LEADS			OCCIPITO-INDIFFERENT LEADS			OCCIPITO-VERTEX LEADS		
	Total	More alpha activity on		Total	More alpha activity on		Total	More alpha activity on		Total	More alpha activity on	
		Right	Left		Right	Left		Right	Left		Right	Left
1.10–1.20	9 (10)	8 (4)	1 (6)	5 (5)	2 (0)	3 (5)	6 (5)	4 (2)	2 (3)	3 (7)	1 (4)	2 (3)
1.21–1.30	6 (1)	5 (1)	1 (0)	5 (5)	4 (1)	1 (4)	2 (7)	0 (6)	2 (1)	3 (4)	2 (2)	1 (2)
1.31–1.40	2 (1)	0 (0)	2 (1)	6 (1)	6 (0)	0 (1)	0 (0)	0 (0)	0 (0)	3 (1)	2 (1)	1 (0)
1.41–1.50	7 (2)	5 (1)	2 (1)	4 (4)	2 (1)	2 (3)	3 (3)	1 (1)	2 (2)	1 (5)	1 (2)	0 (3)
1.51–1.90	2 (3)	1 (1)	1 (2)	2 (3)	1 (2)	1 (1)	1 (4)	1 (2)	0 (2)	1 (0)	1 (0)	0 (0)
2.00	0 (0)	0 (0)	0 (0)	1 (2)	1 (1)	0 (1)	0 (0)	0 (0)	0 (0)	0 (2)	0 (2)	0 (0)
Over 2.00	0 (1)	0 (1)	0 (0)	0 (4)	0 (2)	0 (2)	0 (4)	0 (4)	0 (0)	0 (2)	0 (2)	0 (0)
Over 1.10	26 (18)	19 (8)	7 (10)	23 (24)	16 (7)	7 (17)	12 (23)	6 (15)	6 (8)	11 (21)	7 (13)	4 (8)
Over 1.20	17 (8)	11 (4)	6 (4)	18 (19)	14 (7)	4 (12)	6 (18)	2 (13)	4 (5)	8 (14)	6 (9)	2 (8)
Over 1.50	2 (4)	1 (2)	1 (2)	3 (9)	2 (5)	1 (4)	1 (8)	1 (6)	0 (2)	1 (4)	1 (4)	0 (0)
2.00 or more	0 (1)	0 (1)	0 (0)	1 (6)	1 (3)	0 (3)	0 (4)	0 (4)	0 (0)	0 (4)	0 (4)	0 (0)

Figures indicate number of subjects.
Figures in parentheses—Cases with cerebral pathology (Part II).
Other figures—Control cases (Part I).

cerebral pathology. The subjects included: 20 patients complaining of headache; 11 patients with hysteria and psychoneurosis; 11 patients complaining of dizziness and syncope; 11 patients with idiopathic epilepsy; 10 patients with neuritis; 8 patients with spinal cord disease; 3 patients with myasthenia gravis; 2 patients with hypertension; 2 patients with peripheral arteriosclerosis; 1 patient with Paget's disease; 1 patient with hypoglycemia; and 1 patient with obesity. No delta activity was present in the record of any of these patients. All the patients were right-handed.

Index of asymmetry: The "index of asymmetry" was determined by dividing the per cent alpha time, corresponding to the hemisphere with the greater amount of alpha activity, by the per cent alpha time of the symmetrical lead from the other hemisphere. Bursts of at least 3 waves of a frequency from 8 to 12 per second and of at least 10 microvolts amplitude were considered as alpha activity.

Results: Table 1 shows the number of cases in which the various indices of asymmetry of 1.1 and more occurred in the parietal and occipital regions and also shows the distribution as to the two sides. Table 2 shows the percentage of total number of cases in which the various indices of asymmetry occurred.

TABLE 2

INDEX OF ASYMMETRY	PARIETO-INDIFFERENT LEADS	PARIETO-VERTEX LEADS	OCCIPITO-INDIFFERENT LEADS	OCCIPITO-VERTEX LEADS
1.10–1.20	11 (20)	6 (10)	7 (10)	4 (14)
1.21–1.30	7 (2)	6 (10)	2 (14)	4 (8)
1.31–1.40	2 (2)	8 (2)	0 (0)	4 (2)
1.41–1.50	9 (4)	5 (8)	4 (6)	1 (10)
1.51–1.90	2 (6)	2 (6)	1 (8)	1 (0)
2.00	0 (0)	1 (4)	0 (0)	0 (4)
Over 2.00	0 (2)	0 (8)	0 (8)	0 (4)
Over 1.10	31 (36)	28 (48)	14 (46)	14 (42)
Over 1.20	20 (16)	22 (38)	7 (36)	10 (28)
Over 1.50	2 (8)	2 (18)	1 (16)	1 (8)
2.00 or more	0 (2)	1 (12)	0 (8)	0 (8)

Figures indicate approximate percentage of total number of subjects.
Figures in parentheses—Cases with cerebral pathology (Part II).
Other figures—Control cases (Part I).

The tables show the following facts: Considering values above 1.1 only, there is an asymmetry in alpha activity of symmetrical regions in about 30 per cent in the parietal region, and in about 14 per cent in the occipital region. Values above 1.2 were found in about 20 per cent of the cases in the parietal region and in about 7 to 10 per cent of the cases in the occipital region. More alpha activity occurs more frequently in the right than in the left parietal region. The number of cases with asymmetry in the occipital region is not sufficient to establish a lateral predominance.

Comparison of the indices for parieto-vertex, parieto-indifferent and parieto-occipital leads shows: Out of 18 cases with indices of asymmetry above 1.2 in parieto-vertex leads, 15 showed more alpha activity in parieto-indifferent leads on the same side also. These indices for parieto-indifferent leads were above 1.2 in 11, and between 1.1 and 1.2 in 4 cases. In no case in which less alpha activity was found on one side in parieto-indifferent and parieto-vertex leads, was there more alpha activity recorded in the parieto-occipital lead of the same side. Therefore, our results cannot be explained by asymmetrical placement of corresponding electrodes.

There was a relatively low correlation in this group of patients between the indices of asymmetry obtained in the parietal and occipital regions respectively. Only in 3 cases of 18 showing indices above 1.2 in parieto-vertex leads were there similar indices in occipito-vertex leads. Four of these 18 patients showed indices between 1.1 and 1.2 with more alpha activity on the side on which there was more alpha activity in parieto-vertex leads.

Indices of asymmetry above 1.2 in the parietal region were found in: 4 patients complaining of headache; 1 patient complaining of syncope and dizziness; 1 patient with hysteria; 1 patient with epilepsy; 2 patients with neuritis; 1 patient with spinal cord disease; 2 patients with hypertension; 2 patients with arteriosclerosis; 1 patient with Paget's disease; 1 patient with obesity. This group of patients presented, therefore, essentially the same distribution of disorders as the original group.

DISCUSSION

Our findings show that differences in bilateral alpha activity with indices up to 1.5 are not infrequent in cases without evidence of focal or diffuse cerebral pathology, that higher values are rare, but that even an index of 2.0 in one lead may occur in such cases. The frequent occurrence of less alpha activity on the left side suggests that this finding is related to the dominance of the left hemisphere.

PART II

The same measurements as described in Part I were performed on the records of 52 cases of cerebro-vascular disease and multiple sclerosis none of which showed delta activity. For the description of the results the cases are arranged in 5 groups.

Group 1. Multiple sclerosis: This group consisted of 12 cases. Three cases showed indices of asymmetry higher than 1.5, 2 of them in one lead only, 1 in two leads. Only in one case the index of asymmetry was higher than 2 (2.5) and this in one lead only.

Group 2. Diffuse cerebro-vascular disease: This group consisted of 20 cases in which the symptomatology pointed to changes in both hemispheres. The diagnosis was cerebral arteriosclerosis and hypertensive encephalopathy in 14 cases, cerebro-vascular syphilis in 6 cases. An index of asymmetry higher than 1.5 occurred in 4 cases, out of which 1 showed an index of 2.0, 2 an index of 2.5, each time in one lead only.

Group 3. Vascular lesions of the brain stem: This group consisted of 3 cases. In no case an index of asymmetry higher than 1.5 was found in any one lead.

Group 4. Old vascular lesions of one hemisphere: This group consisted of 3 cases with hemiplegia of more than one year's duration. The symptomatology pointed to lesions in one hemisphere only. All the indices of asymmetry were below 1.5 except in one case where there was an index of 1.6 in one lead.

Group 5. Recent vascular lesions of one hemisphere: This group consisted of 14 cases, 10 of which were diagnosed as cerebral thrombosis, 3 as cerebral embolism, 1 as cerebro-vascular spasm on an allergic basis. The interval between the onset of symptoms and the electroencephalographic recording was 2 days to 10 weeks. Indices of asymmetry higher than 1.5 were found in 7 cases: in 2 cases they were 1.7 and 1.8 respectively in one lead only, in one case an index of asymmetry of 2.0 occurred in 3 leads, in 4 cases indices of asymmetry higher than 2 were observed. The amount of alpha activity in all these cases was smaller on the side on which the lesion had to be localized from the clinical symptoms. No correlations between the electroencephalographic findings and the type of symptoms and their duration could be found within this group. Six cases showed homonymous hemianopsia. Only two of them showed indices of asymmetry higher than 2.0.

Tables 1 and 2 give further information about the distribution of the various indices of asymmetry among the cases of Part II.

DISCUSSION

Table 2 shows that the average degree of asymmetry in alpha activity is larger in the cases of Part II than in those of Part I. This is particularly evident for values above 1.5 which occur only very rarely in the control group (1–2 per cent). Therefore an index of asymmetry of 1.5 or more, particularly if occurring in more than one of the leads employed, must be suggestive of cerebral pathology even in the absence of delta activity. On the other hand values between 1.5 and 2 (the latter in one lead only) occur also in cases without evidence of cerebral pathology. Therefore only an asymmetry index of 2 in more than one lead or an asymmetry index of more than 2 in any one lead can be considered as a definite sign of cerebral pathology.

Such values were obtained only in 8 out of 52 cases with cerebro-vascular lesions and multiple sclerosis. The absence of such a degree of asymmetry and of delta activity does not prove the absence of cerebral pathology. Abnormally high degrees of asymmetry in alpha activity are found most frequently in recent cerebro-vascular lesions with involvement of one hemisphere only (5 out of 14 cases). This indicates that the localized depression of alpha activity in these cases is only temporary.

SUMMARY

1. An index of asymmetry in bilateral alpha activity is defined.

2. Cases without indication of focal or diffuse cerebral pathology showed a definite bilateral difference (index of asymmetry 1.2 or more) in the alpha

activity recorded from the parietal region in about 20 per cent of the cases, while a similar bilateral difference occurred in the occipital region in about 7 to 10 per cent of the cases. Less alpha activity occurred more frequently on the left than on the right, at least in the parietal region.

3. While indices of 1.5 or more are rare in the control group and must therefore be suggestive of cerebral pathology, particularly if occurring in more than one lead, only an index of asymmetry of 2 in more than one lead or an index of asymmetry of more than 2 in any one lead can be considered a sign of cerebral pathology.

4. Out of 52 cases with cerebro-vascular disease only 8, including 5 cases with recent vascular lesions of one hemisphere, showed such a degree of asymmetry. Its absence cannot be used to rule out cerebral pathology.

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CHOLECYSTITIS AND CHOLELITHIASIS IN CHILDHOOD

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Calculus cholecystitis is primarily a disease of middle age. It is uncommon, although not a rarity, in early adult life. In childhood this lesion is most unusual. It would seem worthwhile therefore to report an instance of cholecystitis and cholelithiasis recently seen in a girl aged twelve years.

CASE REPORT

History (Adm. 468527). A. B., a female child, aged 12 years, was admitted to The Mount Sinai Hospital on January 29, 1941. Three days previously she had awakened with epigastric pain, nausea and vomiting. The pain shifted to the right upper abdominal quadrant where it persisted, extending laterally along the right costal margin.

During the preceding year the patient had experienced three attacks similar to the present illness each of which subsided spontaneously in a few days. Jaundice had never been noticed.

At the age of five years she had acute rheumatic fever. The parents were aware of a cardiac valvular lesion resulting from that illness. Past illnesses included uncomplicated mumps, measles, and scarlet fever in early childhood.

Examination. The patient was a somewhat obese child, normally developed for her age. She appeared acutely ill but only moderately uncomfortable. The rectal temperature was 98.6°F. The pulse rate was 84 and the respiratory rate was 20 per minute. The skin and sclerae were normal in color. The cardiac outline was found enlarged to the left on percussion. A loud soft systolic murmur was audible over the entire precordium, heard best at the apex and transmitted toward the left axilla. The lungs were clear. The extremities were negative. The abdomen was moderately distended. Tenderness and muscle spasm were elicited over the right upper abdominal quadrant. Generalized rebound tenderness was present. Rectal examination was negative.

Laboratory data. The white blood cell count was 20,800 with 90 per cent polymorphonuclear leucocytes. The icterus index was 4. The urine was negative.

Course. Despite the youth of the patient, a tentative diagnosis of acute cholecystitis was made although the possibility of infection of a high-lying appendix could not be excluded. Recurrence of acute rheumatic fever with abdominal manifestations was also considered but thought to be unlikely. It was felt that further observation was warranted.

Eight hours after admission, the temperature rose to 102.8°F. The leucocytosis increased. Abdominal pain, tenderness, and muscular rigidity became greater in degree and extent. Operative intervention was then carried out.

Operation. Under ethylene and ether anesthesia, the abdomen was opened through an upper right rectus muscle splitting incision. The peritoneal cavity contained a small amount of clear, free fluid. A greatly distended, thickened and inflammed gall bladder was found. There was striking edema of the contiguous retroperitoneal tissues. Dark, purulent bile was obtained on aspiration of the gall bladder, which also contained many calculi, several of which were impacted in its ampulla. The common duct was not dilated and was negative to palpation. Retrograde cholecystectomy was done. Two Penrose drains were placed down to Morrison's pouch. The abdominal wall was closed with steel wire sutures for peritoneum and fascia, and pincetts for the skin.

Pathologic report. "The specimen consists of a resected gall bladder measuring 8 x 4.5 x 1.5 cm. The external surface is markedly injected and varies from bright red to reddish-black in color. The wall is thickened and granular; on section it measures 4 mm. in thickness. The mucosal surface presents the usual feathery marking and is dark green in color.

It contains 28 yellow-orange, raspberry shaped calculi. Diagnosis: Acute Phlegnonous Cholecystitis and Cholelithiasis." The bile yielded diptheroids on culture.

Subsequent course. The temperature subsided gradually, remaining normal after the sixth postoperative day. The patient left the hospital fourteen days after operation at which time the operative wound was firmly healed. Aside from a later readmission to the Hospital for an unrelated illness she has since remained well. When last examined in November 1941, ten months after operation, she was entirely free of abdominal symptoms.

COMMENT

Up to a relatively short time ago, inflammatory disease of the gall bladder occurring in children was generally regarded as a pathological and clinical curiosity. The earlier medical literature contains only sporadic records of such findings, usually dealing with single case reports or limited compilations of such experiences. Almost invariably such accounts cite the case of Gibson (1), in 1722, as the earliest published record of cholecystitis in a child. So consistently is this case referred to by writers on this subject that it has become a traditional example of early clinical observation. Hence it was not a little disappointing that Gibson's report was found, on investigation, to deal with an instance of hepatosplenomegaly with marked ascites probably due to intrinsic hepatic abnormality, but evidently not an example of biliary tract disease as the term is generally used today.

In 1899, Still (2) reported 20 cases of biliary calculi in children, which had appeared in the literature from the time of Gibson and added 3 cases of his own. During the following two decades, only isolated case studies appeared. In 1923 Kellogg (3) collected 64 cases of gall bladder disease in childhood, and Beals (4) in 1928 brought the compiled total to 124. It is somewhat surprising, therefore, to find Potter's paper (5), published the same year, recording 226 collected cases of cholecystitis in young subjects under the age of fifteen years. The same author (6), ten years later, had increased his series to 432 cases including ten of his personal experience.

Thus there has evolved the recent belief that childhood cholecystitis is of fairly frequent rather than rare occurrence. Where scarcely more than a decade ago the authoritative textbooks on Pediatrics dismissed this subject with only brief mention as practically non-existent, later writers, evidently influenced by Potter's statistics, have gone to the other extreme. A recent paper (7) states that the collected cases probably represent but the "merest fraction of the actual number of children afflicted."

The impression created by the weight of accumulated statistics is evidently considerable. Critical analysis however shows that these reports are liable to misinterpretation. Included in Potter's compiled series are many instances, amounting to nearly one-third of the total number, of fetal and neonatal abnormalities of the biliary tract discovered upon post-mortem examination. This series also lists many other lesions not usually regarded as gall bladder disease including the following examples: hepatic cirrhosis (6 cases), cholangitis, hemolytic jaundice, blood dyscrasias, foreign bodies in the bile passages, parasitic disease, common duct trauma, neoplasms and tuberculous adenopathy. Diag-

nosis was made from symptoms alone, unconfirmed by operation or autopsy, in 21 of the 226 cases in the first series. Cholecystectomy was performed in less than 35 cases. Of this author's six personally observed cases reported in 1938 only one was brought to operation; one was a premature infant with congenital atresia of the common duct; and in the remaining four cases, the cholecystitis was postulated because of the presence of abdominal pain or icterus.

On the basis of age, etiologic factors, treatment and prognosis, childhood cholecystitis may be classified as of three distinct varieties.

In infancy and early childhood biliary disease is usually due to congenital malformation of the bile passages. The biliary tract is subject to various developmental defects consisting of narrowing, atresia or absence of portions of the duct system. Concretions in the gall bladder or bile ducts discovered in such instances are generally the products of inspissated bile pigment differing in chemical composition from true gall stones. The viscosity and stagnation of bile in fetal life are believed to be further factors in their formation. These patients are rarely amenable to relief by surgical measures.

Inflammation of the gall bladder in later childhood is most frequently the result of systemic infections, giving rise to acute cholecystitis which may go on to suppuration but which, as a rule, subsides spontaneously. The formation of calculi is exceptional and subsequent chronic cholecystitis of this origin is unlikely.

In the case here reported, acute exacerbation of chronic cholecystitis with cholelithiasis occurred. This child had the adult type of gall bladder disease, the underlying basis of which is generally believed to be a metabolic disorder. Such instances are still rare in childhood but they do occasionally occur even in the very young. The symptoms are similar to those seen in adults. The diagnosis is usually rendered difficult because the possibility of gall bladder disease occurring in young patients is not usually entertained. This applies particularly to the chronic cases where the chief symptoms are liable to be vague and in children may be considered functional in origin. When accompanied by jaundice these are often classed as "catarrhal icterus". It is quite probable that some cases of gall bladder disease discovered in later life have their inception in childhood. The more frequent employment of cholecystograms might explain some of the indefinite digestive disturbances of children on this basis. Treatment is, as a rule, operative, cholecystectomy being required to prevent recurrence of the cholecystitis and the complications of cholelithiasis.

SUMMARY

A case of acute gangrenous cholecystitis with cholelithiasis, occurring in a girl of 12 years, is presented.

The problem of biliary tract disease in infancy and childhood is discussed and the literature on this subject is briefly reviewed.

This patient presented the adult type of gall bladder disease which is rarely seen in children, although it most likely has often gone unrecognized.

It seems not improbable that some of the biliary tract diseases of later life

have their inception in childhood cholecystitis. Earlier recognition of the disease in those cases might serve to prevent some of the complications and sequelae of biliary tract disorders seen so frequently in adults.

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A BRIEF INTRODUCTION TO AVIATION MEDICINE*

ALAN LESLIE, Lt. MC-USNR

In aerial flight the human organism is exposed to a source of physical and psychic stresses untapped prior to the advent of the aeroplane. Although Tissandier and his unfortunate companions experienced a dramatic demonstration of the effects of anoxia (loss of consciousness and death, respectively) during a balloon ascent to high altitude, the physiological problems were of little general importance before commercial and military aviation attained their present universality. With continued progress a greater proportion of the general population will become involved. Increasing mechanical perfection of aeroplanes, with consequently greater speed, attainable height, and maneuverability have enhanced the degree and extent of the problems. In the routine of commercial air transportation they are fairly well stabilized, but in military aviation they are of the utmost importance.

The human organism has had no evolutionary preparation or selection to enable it to cope satisfactorily with these new hazards. For instance, the normal carotid body response to the anoxia attendant on ordinary physical exercise is a physiologic hyperpnea which is maintained up to the point of liquidation of the oxygen debt. On the other hand, hyperventilation, a response mediated by the carotid body to the anoxia of high altitude, is not only of no benefit but actually dangerous, occasionally resulting in acapnic alkalosis with its separate symptomatology. The reason that this occurs in the latter situation is that at high altitude the partial pressure of oxygen is insufficient to effect the normal saturation of the arterial blood, and no amount of overbreathing will overcome this. Under normal circumstances, labyrinthine, visual, and kinesthetic impulses are synergistic for the maintenance of equilibrium. Seasickness and, to a greater extent, airsickness follow the dissociation of these impulses. This dissociation may become extreme in aerobatics and require suppression of the labyrinthine impulses and perhaps the kinesthetic impulses as well for the maintenance of proper orientation in space and the prevention of airsickness. In commercial flying the effects of acceleration are of little consequence. These become apparent only when there is a rapid change in linear motion, either in speed or direction, so that the effects of inertia are realized. Combat flying frequently requires violent maneuvers. The more mobile components of the body, such as the blood, brain, and viscera, both thoracic and abdominal, are naturally first affected by such activity. When, as occurs in the pull-out after a dive, the force of inertia is directed away from the head, there is cerebral and retinal anemia, with attendant darkening or "black-out" of the visual field, with or without fleeting loss of consciousness. If the direction of forces should be reversed, as in an "outside loop," blood remains in the cranium under in-

* The opinions and assertions contained herein are private ones of the writer, and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

creased pressure because of the impaired venous outflow, and there is a "red-out" or red fringe over the visual field. The visceral attachments are subjected to strains for which they were not designed, and the viscera themselves undergo unaccustomed pressures. Since commercial aviation is concerned merely with rapid and safe transportation, the effects of acceleration as just exemplified are minimal and all but imperceptible to the passengers. Greater speed and smoothness of flight are enjoyed at higher altitudes, so the problems interposed by high altitude and altitude changes are of greater importance.

The medical problems arising from man's ascent to unaccustomed altitudes are closely dependent on the physics of altitude, and may be grouped as follows:

1. Problems arising from decreased temperature.
2. Problems arising from decreased barometric pressure.
   a. From decreased partial pressure of oxygen.
   b. From expansion of gases (and contraction on descent).
   c. From dissolved gases coming out of solution.

The atmospheric temperature falls about 1°C. for every six hundred feet of ascent, and at 35,000 feet reaches −45° to −55°C. The problems of heating and clothing are somewhat specialized, but the general medical considerations are no different from those due to low temperatures at sea level.

Lowered barometric pressure produces a set of problems which are specific for aviation. At 18,000 feet the barometric pressure is one-half the sea level value, i.e., 379 mm. Hg instead of 760. With the fall in partial pressure of oxygen in the atmosphere from 160 mm. Hg to 80 mm. Hg, the partial pressure of oxygen in the pulmonary alveoli drops to about 60 mm. Hg, and the saturation of the arterial blood falls to about 65 per cent (from the normal of 95 per cent at sea level). Unless additional oxygen is supplied, there is serious anoxia, leading directly to the symptom-complex of acute altitude sickness. People such as the miners of Peru, accustomed to living at high altitudes, show a compensatory increase of hemoglobin as one important feature of acclimatization, so that despite the decreased percentage saturation of the blood, an adequate total amount of oxygen is present. This compensation is limited so that man's ceiling of acclimatization for normal activity is between 16,000 and 17,000 feet.

According to Boyle's Law the volume of a gas varies inversely with the pressure upon it. Entrapped gases in the body will expand to twice the sea level volume after an ascent to 18,000 feet. Thus there arise problems in nutrition, gas forming foods obviously being ill-advised before an aerial journey. Persons with intestinal obstruction or atony of even mild degree and aerophagics may be acutely uncomfortable on such a trip. Persons under collapse therapy for pulmonary disease will be endangered by the expansion of intrathoracic gas causing displacement of the mediastinum. A small bubble of gas at the site of dental pathology will, in its tendency to expand, exert pressure and cause severe pain. Special problems become apparent in the field of Oto-Laryngology. During ascent the expansion of gas in the middle ear, mastoid cells, and nasal sinuses will generally cause no trouble, since these organs clear themselves by the free egress of the enclosed gas. In the rare instances of almost complete occlusion of an orifice there will be pain due to the increase of pressure exerted

by the entrapped gas. In descent, however, there may be greater difficulty. In order to equalize the pressure which is building up outside the ear, bowing the drum in, and sinuses, air must be forcibly introduced into these cavities. This is especially necessary for clearing the ears, since air will not re-enter the middle ear through the Eustachian tube unless this is consciously opened. Ordinarily, this is accomplished by yawning and swallowing or holding the nose and "blowing"—to raise the pressure in the respiratory tract. When, because of infection or anatomical abnormality, an individual cannot clear his ears or sinuses, acute pain occurs. The ear drum is pressed in, and unless the pressure is equalized, eventually ruptures. Aero-otitis media may follow lesser trauma to the drum. This is characterized by a fiery red injection of the drum and a sero-sanguinous exudation into the middle ear cavity. This usually subsides with expectant treatment, myringotomy being contra-indicated, unless there is definite pus formation. Shrinkage of the nasopharyngeal mucosa by the use of any of the common vasoconstrictors will usually prevent or alleviate this type of difficulty. Otherwise there must be reascent to such an altitude as is necessary for the equalization of the pressure; cautious descent may then be reattempted. Persons with upper respiratory infection should not enter aircraft in which rapid descents are contemplated. The slow rate of descent in transport planes will ordinarily cause no difficulty. Sleeping passengers should be awakened during descent so that they may clear their ears and sinuses.

The problems under consideration are magnified by ascent to higher altitudes. At 28,000 feet the barometric pressure is one-third of its sea level value, at 34,000 feet one quarter, and at 42,000 one sixth. Gases expand to three, four, and six times their sea level volumes respectively. Oxygen should be furnished at altitudes in excess of 12,000 feet with appropriate, individually fitted equipment. Above 35,000 feet anoxia will occur even if 100 per cent oxygen is administered, because the total barometric pressure is lower than the critical level of oxygen pressure for the adequate oxygen saturation of the arterial blood. The symptomatology of anoxia and acute altitude sickness in normal individuals will not be described here, since this information is readily available in any modern textbook of Physiology. Chronic altitude sickness is ordinarily not encountered in aviation.

Increased general sensitivity to anoxia frequently accompanies pathologic states. Recent alcoholic excess will lower a person's tolerance to anoxia. Patients with coronary insufficiency, impaired cardiac function, anemia, and pulmonary pathology and persons recently under chemotherapy with sulfonamide or other drugs impairing the oxygen carrying power of the blood should have oxygen supplied from relatively low altitudes (5000 feet). Anginal pain resulting from anoxemia will be promptly relieved by the administration of oxygen. Persons having hypersensitive carotid bodies may show signs of alkalosis due to hyperventilation induced by anoxemia even below 10,000 feet.

The question of aero-embolism ("bends") and aero-emphysema, caused by rapid ascent and decompression, as seen in the diver's caisson disease, is of greater military than civilian importance because of the higher altitudes at which military flying is conducted. Ascent to altitudes in excess of 30,000 feet is

accompanied by the appearance of nitrogen bubbles in the blood stream and also locally in the tissues; in susceptible individuals this occurs at considerably lower altitudes. The severity of this phenomenon is directly proportional to the rate and magnitude of the ascent. The mechanism is the same as that responsible for the appearance of bubbles in a bottle of carbonated water when the cap is removed, namely, a lessening of the external pressure holding the gas in solution. If the bubbles appear in sufficient size and number, symptoms somewhat similar to those seen in divers and caisson workers after too rapid decompression occur, the type of reaction depending on the distribution of the obstructed blood vessels or the site of local liberation of bubbles in the tissues. These manifestations may be rapidly dissipated by descent, which effects recompression, or may be prevented by the preliminary inhalation of oxygen during an hour of exercise. This latter procedure is known as denitrogenation. The symptoms experienced and the approximate order of their appearance are as follows:

1. Cutaneous—there may be generalized itching, paresthesias, hot or cold flashes, a sensation of coolness on the eyeballs.
2. Articular—joint pain involving one or more joints and varying in severity from a dull ache to an incapacitating splinting of the joint.
3. Abdominal—cramps (bends).
4. The "chokes"—uncontrollable cough and wheezing due to the irritant action of bubbles liberated locally in the larynx, trachea, bronchi, and interstices of the lungs.
5. The "staggers"—impairment of equilibrium due to the liberation of bubbles in the semicircular canals or cerebrospinal fluid.

The last two mentioned are infrequent.

All the problems arising from the lowering of the barometric pressure may be avoided by the use of some method for the maintenance of the individual at a pressure equal to or close to that at sea level. This may be accomplished by the use of sealed pressure aircraft cabins or by the use of pressurized clothing in open cockpit aircraft. The former method has been successfully applied in commercial air transportation. It is not necessary to build the cabin to maintain sea level pressure, because for high altitude flight this would necessitate sacrificing weight of pay load for strengthening the plane. A cabin built to maintain an interior pressure corresponding to a pressure altitude of 8000 feet would be entirely practical. Precautions to safeguard individuals unable to tolerate even slight anoxia would still be necessary.

Much of the field of aviation medicine has to do with pilot selection and the maintenance of flying personnel, these problems belonging to the fields of Psychology and Psychiatry, Ophthalmology, and Oto-Laryngology. Psychiatry is an integral sub-specialty in the field of Aviation Medicine. The functional derangements which occur among aviation personnel differ from those common to general practice only in etiology, and with known etiology psychotherapy is usually effective. Air transportation of the sick and wounded is a comparatively recent innovation, and indicates the progressively expanding scope of Aviation Medicine.

CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

Wednesday, October 16, 1940

Spirochetosis Icterohemorrhagica (Weil's Disease)

[*From the Medical Service of Dr. B. S. Oppenheimer*]

History (Adm. 461832; P.M. 11589). A 50 year old sewer worker was admitted to the hospital because of fever and jaundice. His past history was entirely negative. Five days before admission on returning from work, he experienced malaise, headache, aching legs, and feverishness followed by shaking chills. This was diagnosed as the "grippe." The fever and marked prostration continued. Two days prior to admission he developed vomiting and diarrhea, the stools being almost black in color and watery. One day prior to admission jaundice was noted. The muscle pains became more severe. During the twenty-four hours before admission only a small amount of urine had been voided. Although the patient stated he had encountered many rats while engaged in his work, he did not recall having been bitten by any. His room-mate, also a sewer worker recently suffered from fever and jaundice from which he recovered.

Examination. The patient was a gaunt, ruddy-faced, markedly icteric man, prostrated and acutely ill. The temperature was 97.8°F. His pupils were normal. The sclerae were markedly icteric. The tongue was dry and covered with a brown, pasty material. The lungs revealed no abnormalities. The heart appeared to be slightly enlarged to the left. The sounds were of good quality; A2 louder than P2; no murmurs. The cardiac rhythm was totally irregular with a ventricular rate of 146 and a pulse deficit of 26 per minute. The blood pressure was 80 systolic and 45 diastolic. The liver was palpable two fingers below the costal margin; the spleen was not felt. Generalized muscle tenderness was present. A small cluster of pin-point purpuric spots were seen over the lateral aspect of the left knee. The reflexes were hypoactive; there were no meningeal signs.

Laboratory data. Examination of the urine showed a 4 plus albumin, and many red and white blood cells. Hemoglobin, 94 per cent; red blood cells, 4,040,000; white blood cells, 11,100 with 90 per cent polymorphonuclear leucocytes. Blood urea nitrogen, 112 mg. per cent; carbon dioxide combining power, 34 volumes per cent; sugar, 130 mg. per cent; cholesterol, 185 mg. per cent; ester, 45 mg. per cent; and icterus index, 60; total protein, 5.5 grams per cent. Blood Wassermann reaction, negative. Prothrombin index, 70; blood culture, negative. Vomitus and stool gave a 4 plus guaiac reaction. Guinea pigs inoculated with blood and urine died after about two weeks; motile Leptospira were demonstrated by dark field examination of the tissue juice of the guinea pig.

Course. The patient was obviously desperately ill. Numerous frequent watery, black bowel movements occurred. He vomited frequently in small amounts. Because of the appearance of shock, and the rapid uncontrolled auricular fibrillation, he was digitalized, transfused, and given continuous intravenous therapy of 5 per cent glucose in saline. In spite of this, he voided very little urine. Only a few cubic centimeters of urine were obtained by catheter during his hospital course. The blood urea nitrogen mounted sharply to 150 mg. per cent. He was also given vitamins C and K. His respirations became more rapid and shallow. Death occurred forty-eight hours after admission with the picture of uremia.

Necropsy findings. Dr. Klemperer. The *liver* was enlarged, weighing 2170 grams. However, the lobular structure appeared to be perfectly normal, and there was no other gross evidence of hepatic disease. Microscopically there were several striking features: the liver cells, normally contiguous, were separated one from the other by a small clear space; mitotic figures were visible in many of the cells, as well as binucleated cells. The *kidneys*, grossly, showed no evidence of degeneration. No hemorrhages were seen on the surface. They were somewhat larger than normal and edematous. Microscopically, the glomeruli were virtually free of any important lesions; the tubular epithelium showed a moderate degree of degeneration as well as some edema and cellular infiltration. In the *spleen* and *lymph nodes*, one could see many macrophages containing fragments of red blood cells and particles of hemoglobin. Leptospira were found in large numbers in every organ with the exception of the muscles. In the latter sites there were areas of degeneration of the Zenker type. A necrotizing esophagitis of severe degree was found. The lack of any really gross pathological findings is characteristic of this disease. Microscopically, the liver showed what is most often found in this condition, namely: dissociation of the cells, mitosis and amitosis. The renal findings are entirely too little to account for the renal shutdown; the functional damage is out of proportion to the morphological change. The icterus is another feature that is difficult to explain. There is very little tangible liver cell damage but the dissociation of the liver cells may disrupt the continuity of the bile capillaries. Another possible explanation is that the jaundice is at least partly of a hemolytic nature; this contention is supported by the finding of macrophages with ingested red blood cells.

Comment. Dr. Tiffany. This disease appears to be on the increase. We have records of twelve cases reported in New York City in the last ten years. It is disseminated by wild rats who are infected with the causative organism. The leptospira are found on the surfaces of their renal tubules and are excreted through the urine. The organisms may live outside of the body for some time. Thus actual contact with the rat is not essential, the disease being contracted by contact with rat excreta. For this reason one would expect to, and one does, find the disease most commonly in sewer workers, dish-washers, etc, who work in rat infested surroundings.

The final, differential diagnosis of this disease can be established only by laboratory examinations. These include direct demonstration of the organism in the circulating blood or in the urine: this fails most of the time. Or one may test the patient's serum for specific antibodies against the Leptospira; however, these do not appear until the seventh to tenth day. They then continue to rise and may reach a titer of 1:50,000. Unfortunately, this is not diagnostic since high titers may be retained for many years. A 1:1000 positive dilution is highly presumptuous.

The third method of laboratory investigation is the best. It consists of inoculating small amounts of blood or urine intraperitoneally or intramuscularly in a guinea pig. The infected animal then develops listlessness and fever. About the seventh day icterus develops. At this stage the Leptospira are demonstrable in the circulating blood. The temperature then sharply drops to subnormal limits (reminiscent of the case under discussion here) and the animal dies in twenty-four hours. Aside from petechiae and icterus, the characteristic postmortem finding is a hemorrhagic mottling of the lung surfaces, often referred to as "butterfly spots."

A fourth method is direct blood culture, which is attended by many difficulties.

In humans, the incubation period is about 10 days. Oftentimes an erythematous maculo-papular rash will appear around the third week of the disease.

Dr. Baehr. The case represents the typical clinical picture of very severe Weil's disease. In fact, the damage to the kidneys and the liver was so intense that one can well see how a mistaken diagnosis of yellow fever is possible. The rapid, fatal termination after only seven days of illness amply attests to the overwhelming infection in this instance. I should like again to emphasize that there is no necessity for actual contact with a rat in order to contract the disease; the portal of entry is through the skin and hence contact with the excreta of rodents is sufficient. This is possible in sewer workers. Although sewer workers are protected by rubber boots, they often work with ungloved hands which are apt to be bruised and which come into contact with rat excrement.

Reported by *Max Ellenberg, M.D.*

DR. BARNEY (BERNARD) SACHS ANNIVERSARY VOLUME PRESENTATION

On November 24, 1942, on the occasion of the sixtieth anniversary of his active participation in the practice and the science of medicine, Dr. Barney Sachs was presented with a special issue of the Journal of The Mount Sinai Hospital dedicated to him by his colleagues, associates and friends. The celebration was attended by a large gathering in which men prominent in medicine, former associates and pupils, as well as many close friends and admirers of Dr. Sachs were present.

The meeting was opened by the President of The Mount Sinai Hospital, Mr. Leo Arnstein. He was followed by others who spoke of the high esteem in which Dr. Sachs is held by all and of the great contributions Dr. Sachs has made to medicine, to related fields and to the various communal institutions with which he has been connected.

Dr. Sachs spoke in reply, and his exceedingly significant remarks closed a meeting the cordiality and sincerity of which has left a lasting impression on all those who were present.—Ed.

Mr. Leo Arnstein:

It is a great privilege to welcome Dr. Bernard Sachs (who in our affectionate thoughts of him is always "Dr. Barney") on behalf of The Mount Sinai Hospital. It is particularly appropriate that this celebration of the completion of his sixty years of medical humanitarian service to the community should be celebrated in this place, with which he has been so closely identified. So far as I am concerned, the mention of Dr. Sachs' name to me always meant Mount Sinai and the name Mount Sinai meant Dr. Barney Sachs.

Since first, in 1893, he came to Mount Sinai in its former location at Sixty-seventh Street and Lexington Avenue, as a consultant in neurology, through the years when he was appointed as head of the Neurological Service in 1900, and the following twenty-four years during which he built up that Service to its outstanding rank, he has cast luster on the institution. Even after his appointment to the Consultant Staff some sixteen years ago, he has worked with undiminished vitality and produced many important publications so that his reputation has constantly grown.

During the years that he was active on the staff of the Hospital, he not only contributed his time, thought and effort, but also, together with members of his family, gave substantial financial support to the work of the Neurological Division.

On behalf of the Board of Trustees of the Hospital, I extend to him this most cordial greeting and express the hope, which is shared by all of his friends, that he will long continue his fine humanitarian work in the best of health.

Dr. Foster Kennedy:

It is a most happy thing to be able to introduce to you my young friend Barney Sachs. He has few years, but I have many memories. There is no

gossip value in good news, so on the whole I have little to say of him that will satisfy the hunter in any of you, for I have been looking for something evil in him for more than thirty years, and have a completely empty bag.

How is anybody expected to make a successful speech about a man who is loved by the whole world? So Arthurian that it is impossible to throw even a tiny pebble in his direction! The odd thing is that he has achieved a successful life on a foundation of virtue. Most distinguished and successful men have a streak of mystery somewhere within them; but this man is pellucid clear. On a base, clear as pressed glass, there has been built a notable life; not by a long way yet run.

I make oblation to him as the founder of the first neurological service in a great general hospital in the City of New York; and an oblation to him as one of my predecessors in Bellevue.

I am glad to be allowed to take a part in this occasion; to honor a man who has shown me nothing but consideration and kindness for the thirty-two years I have been in this great country, which is now my own.

Doctor Ernest Sachs of St. Louis, Doctor Bernard Sachs' nephew, now President of the American Neurological Association, has asked me, as one of his recent predecessors, to present the compliments and regards of that Association to Doctor Sachs.

Times being what they are, trains being as chancey as they are, gas, having followed its nature—evaporated—and priorities being always with us, Doctor

Sachs could not reach New York to do this happy thing himself; so, I, instead of your nephew, give you, Doctor Sachs, these affectionate wishes and regards from the American Neurological Association.

It is a fine thing, both for you and for him, to be able, regarding yourself and your collateral relations, to know that you are each and together, members of a dynasty!

Dr. Malcolm Goodridge:

When I was born Dr. Sachs was fifteen years old. At that period of our lives there was a great disparity in our ages but I must have been gradually catching up for today as I look back sixty years to the days when I was a boy of ten it seems a very short time indeed. I am therefore not so much impressed with Dr. Sachs' sixty years in medicine as I am with what he has accomplished in those years. We think of eighty-five years as representing advanced old age while as a matter of fact old age does not necessarily have anything to do with years. A man who has something of the youth in him never grows old.

Dr. Sachs became a Fellow of the New York Academy of Medicine in 1887, fifty-five years ago and but three years after he began the practice of medicine. I believe I am correct in stating that this is the oldest connection of his medical career.

In 1912 The Committee on Public Health Relations was established by the Academy. Dr. Sachs was appointed to its membership two years later and served without interruption until 1938. During this twenty-four year period he served as the chairman of two subcommittees whose investigations made very significant contributions to the health and welfare of this community. In 1928 he was appointed chairman of the Committee of Twenty on Street and Outdoors Cleanliness and due in large measure to his personal leadership and to his crusading spirit and zeal the city authorities finally introduced much needed improvement in street cleaning equipment and employees in the Department of Sanitation were trained in modern street cleaning methods.

In 1935 a subcommittee was appointed to study the Domestic Relations Court with special reference to the Children's Court. Dr. Sachs was its chairman. A comprehensive investigation was made with the enthusiastic cooperation of Chief Justice Hill and his Associate Justices. The recommendations made by Dr. Sachs' committee brought about such changes in procedure both with reference to the psychiatric clinic connected with the court and in the understanding on the part of probationary officers as to their duties and function that the number of cases appearing before the Children's Court was reduced by fifty per cent.

He has also served as chairman of the Committee on Honorary Fellowship and Medal and on the Committee to Investigate Problems Relating to Medical Practice.

Dr. Sachs was elected President of the Academy in 1932. He became its Treasurer in 1936. He was a Trustee for a period of fifteen consecutive years ending in 1942 and during most of this time he was a member of the Executive Committee of the Board. In whatever capacity he has served the Academy he

has discharged his obligations with great honor to himself and profit to the institution.

I did not however accept the invitation of Dr. Globus to speak here this afternoon for the sole purpose of recounting the contributions Dr. Sachs has made to the Academy during his more than half a century of Fellowship. I am here also because of the opportunity it affords me to acknowledge my gratitude for the comfort and encouragement he gave me during my first year as President of the Academy. I shall never forget and I shall never cease to be grateful to him for the kindly pats on the back he gave me from time to time, the pats always accompanied by some such words as "you are doing very well, young man." He was a wise enough psychologist to sense my feeling of inadequacy.

It gives me great satisfaction to proclaim my friendship for Dr. Sachs, a sentiment which I am sure I have made him feel ere this.

Dr. Adolf Meyer:

With my congratulations to those who have taken the initiative to honor Bernard Sachs, and to allow us to share in the consideration of a noteworthy life and career, I am happy to bring my own congratulations to you, Bernard Sachs, for the attainment of this tangible and impressive recognition of a life time of exemplary achievement in neurology, the neurology of the child, and the general setting for the service to man, and his nervous system and to the human person.

In keeping with the spirit of a family that has contributed in such a distinguished way to educational and cultural progress, you have brought your great contribution to the medical services. From the Harvard days through your Strassburg European training, you have come to play an active role in the professional, scientific and teaching life of the New World and the New York Polyclinic Hospital and School up to the leadership in the International Neurological Congress and the New York Academy of Medicine and this Mount Sinai Hospital in which you have created a special neurological division in a distinctive way.

To me the contemplation of this human and professional career has revealed an unusual steady and stabilizing influence in cultivating valuable principles as well as noteworthy specific contributions that showed throughout and up to the service in the Friedsam Foundation and its promotion of welfare and research.

It is a stimulation and an exceedingly gratifying satisfaction to have the privilege of participating in this demonstration of esteem and affection to a leader in the good work and the exemplary achievement. We come to you with wholehearted wishes for years of enjoyment of the traditions of the well earned position in the ranks of the octogenarians in action.

Mr. John S. Burke:

This portrait of Dr. Sachs which is being painted here by his friends would miss something in perspective if it lacked a few strokes from the brush of someone familiar with the Altman phase of his activities. Over a century ago a man was born in New York whose name was Benjamin Altman. He established a business

which still survives, and died about three decades ago. His successor, Michael Friedsam, has been dead, too, over ten years. Both of these men lived beyond the allotted three score years and ten, and though their activities stretched back nearly a hundred years, both were close associates of Dr. Sachs in their high prime and in his full vigor. The merged result of their lives, both in its social and commercial meaning bears clearly the sharp imprint of his personality and character; for both the business which they established, and the social institution which they inaugurated, are as they are in many respects because of his philosophy. And their successor in the third generation considers it one of the high privileges of his life that he knows this uncommon man with respect and affection.

To me he seems like a mountain climber pressing ever onward and upward, with his head toward the stars but his feet on the ground; like a mountain climber, too, he pauses often for rest while he refreshes himself in the contemplation of the truth and beauty and order which God has provided in nature, but which many of us miss with our narrower horizons. Not many men lead lives as happy and wholesome and useful as does Dr. Sachs. Rich in years of experience and fruitful in action he seems to have acquired his wisdom without losing his wonder. Like Chaucer's good clerk, still "gladly would he learn and gladly teach." Not for him the choice in Locksley Hall of "Fifty Years of Europe, or a Cycle of Cathay." Indeed, he seems to eat his cake and have it, for, Deo Volente, he will complete the cycle in his home city which he admires and serves so well. Nature made him a gentleman, and while it is often difficult and sometimes hazardous to alter Nature, he has expanded and deepened that generous endowment by his industry and his respect for the eternal verities. Surely of him it may be said that he has a sound mind in a sound body.

I have told him and without denial that his philosophy is well expressed in the words which his old acquaintance, the poet Browning, spoke through the sage, Rabbi Ben Ezra:

> "Grow old along with me, the best is yet to be
> The last of life for which the first was made,
> Our times are in His hand, Who saith a whole I planned,
> Youth shows but half; Trust God, see all nor be afraid."

Mr. Henry L. Moses:

Personally and as President of Montefiore Hospital, I am proud to take part in this deserved demonstration of the respect and affection with which all members of the medical profession regard our honored guest.

Dr. Sachs, your outstanding contributions to medicine as an experienced and beloved clinician, inspiring teacher, and investigator at the bedside and in the laboratory, your unselfish cooperation in educational and research activities in every branch of your profession, your active support of every good cause, the great honors deservedly bestowed upon you by hospitals, universities, medical societies and associations, both national and international, are well known to all who have followed and admired your distinguished career. Of equally great

importance to us who have been closely associated with you is and has been your untiring zeal through your active life in encouraging the young and older physician, physicist, and research worker, not alone with material assistance, which is very often imperative, but even more by your sturdy friendship, your complete sympathetic understanding of their struggles and problems, the joy of your companionship, and your unselfish loyalty, which have cheered, encouraged and inspired many promising men and women to better and nobler achievements.

We at Montefiore are deeply grateful to you for over fifty-three years of productive service and stimulating leadership. You have demonstrated to us by your continuous interest that a consultant may be something more than a physician who, after having given many years of fine service to a hospital, has reached the age of retirement and, therefore, is entitled to enjoy a well earned rest. You refused to be inactive and in the vernacular of baseball, you objected to being retired to the players' bench.

Fully respecting the rules and restrictions applicable to consultants, you have continued a live, helpful interest in the problems of the Hospital by making constructive suggestions about the operation of its services so that it may better discharge its charitable and educational responsibilities. In recognition of this unique service and the important contributions you have made over a period of years, Montefiore created in 1941 a new position of Senior Consultant and at the same time appointed you Senior Consultant in the Division of Neuropsychiatry which you, at the age of over eighty-three, together with a small group, initiated, championed and succeeded in forming but whose operation has unfortunately, due to Pearl Harbor, been postponed for the duration.

Montefiore extends to you its felicitations and congratulations on this auspicious occasion with every good wish that Mrs. Sachs and you may enjoy many, many more years in the fullness of health, happiness and contentment.

Dr. Tracy J. Putnam:

Nothing could be more appropriate than to have a famous hospital celebrate the sixtieth year of practice of its most famous consultant. It is an accomplishment to have striven for three score years in any profession, but Dr. Sachs has done far more than simply to endure. He has been a pioneer and a leader from the beginning of his practice.

He was a young man when he chose to study the science of neurology, and it must have seemed an unpromising field at that time. Neurology used to be defined as that branch of medicine which studies the cases that other doctors do not wish to be troubled with.

But the eye of the pioneer sees deeper than the surface. Dr. Sachs evidently realized that there were further possibilities in neurology; that it might change from a system of diagnosis alone, to become a real science of the structure and function of the nervous system, and of the mechanism and rational treatment of the diseases which affect it. And it is no small part through his efforts that the change has come about. The titans of neurology were alive when he entered practice, and he participated in its heroic age. In these days when neurology is

a comfortable workaday discipline, not without its problems to be sure, but no longer an adventure, we sometimes forget the struggles of our predecessors who made it what it is.

Every civilized man has the duty of being a good citizen, of taking an intelligent part in attacking the problems of his community and country. This Dr. Sachs has always done.

Every true physician aspires to the ideal of being a good practitioner of medicine. Crowds of patients testify to the success which Dr. Sachs has had in his practice.

But to be a doctor means also to be a teacher. Many of us here were children when Dr. Sachs began his teaching career, and he has been busy at it ever since; teaching not only students but physicians whose training is never finished.

Further, a physician is a scientist, who not only learns his subject, but adds to the world's knowledge. A long list of original publications, and the fact that an important disease bears his name, testify Dr. Sachs' ability as an investigator.

Yet even this does not exhaust the true scientist's ideals. To bring together diverse groups, and workers in various countries, to strive together for common ideals, or the ultimate end towards which we all should look, and here, too, Dr. Sachs has been outstandingly successful. That he may succeed once more in uniting the neurologists of the world after the present war, is my sincerest hope.

Dr. Henry A. Riley:

I too can state that it is a great honor and a greater pleasure to have been asked to join and participate in this gathering. I too would add to the encomiums resting on your brow placed there by your many friends and admirers. The majority of the speakers who have preceded me have spoken of the honors which have been yours in this, your own country, but I would call attention to the fame and reputation which you bear in foreign lands. Your international reputation is based on many happy facets of your "total personality" and on your many achievements. Known internationally as one of the discoverers of Tay-Sachs disease, your papers, monographs and books have made your name familiar to an international audience. The series of events which brought you into personal contact with a great number of eminent foreign neuropsychiatrists constitute the successive gatherings of the International Neurological Congresses. The first congress of this kind was to have been held in Paris in 1914. The first world-wide conflagration swept away this plan. The fourth congress was to have been held in Paris in 1943, but it would seem that the present, second world-wide madness will prevent this meeting. No effort was made until 1927 to organize any international neurological meeting, but late in 1926, the idea of holding a joint meeting of the American Neurological Association and the neurological section of the Royal Society of Medicine was broached by Weisenburg, Tilney, Dana and Sachs in this country and Purves-Stewart and Wilson in England. This meeting was held in the summer of 1927 and was a great success. The following year Dr. Sachs met Dr. Marburg at Bad Gastein and in their conversations, the topic of neurology and its advancement held a prominent place. A congress was thought to be the best method of enhancing the prestige

and importance of neurology and it was decided that the American Neurological Association could best bring forward this proposal. In 1928, Dr. Sachs proposed to the Association that the neurological associations and the various universities of the world should be canvassed in order to bring this plan to their attention and to ask them for their support. The response was universally in the affirmative, each country chose committees and elected delegates and in the summer of 1929 a program-executive committee meeting was held in Berne. Dr. Sachs was elected the first President of the Congress and I was elected as the Secretary-General. Plans were made, topics were chosen and Berne was selected as the place for the Congress. During the next year, by continuous effort, contact was established with neurological groups all over the world and so enthusiastic was the response that over 800 neurologists and neurological surgeons, with their families, gathered for the First International Neurological Congress in Berne in the summer of 1931.

The whole tone of the Congress was set by the graceful and friendly opening speech of the Congress by Dr. Sachs. He presided with dignity and ease and the regular social events were amplified by luncheons and dinners given by him. The success of the Congress was preeminently due to him, and through it he became personally known as a kindly, courteous, efficient scientist to as wide an audience as any neurologist has ever reached. The further Congresses owed much to Dr. Sachs and he was elected to and still holds the position of First Honorary President of the Fourth International Neurological Congress.

My other function this afternoon is to bring greetings and felicitations from the Neurological Institute of New York. The Institute owes much to Dr. Sachs who organized the present Children's Service and acted as its Senior Attending for many years. This service has added greatly to the prestige of the Institute and the Institute is greatly beholden to Dr. Sachs for the inspiration and organization of this service. Dr. Sachs also served for a considerable time on the Board of Trustees of the Institute before its closer affiliation with the Columbia-Presbyterian Medical Center. We are still proud of Dr. Sachs' continuing interest in the Institute. The Medical Board, wishing to send its greetings to this gathering and express some of its appreciation and devotion to Dr. Sachs, passed the following resolution which was formulated by Dr. Casamajor, Dr. Sachs' successsor in charge of the Children's Service:

"The members of the Medical Staff of the Neurological Institute can appreciate fully the debt the Institute owes to Dr. Bernard Sachs.

"In our early days when the Institute was struggling for recognition, Dr. Sachs participated actively on our Consulting Staff, encouraged us and threw in our favor the weight of his influence.

"During the trying times of the early nineteen thirties when things looked dark for the Institute and many other hospitals were closing their doors, Dr. Sachs accepted an appointment to our Board of Trustees and helped to steer the Institute through those lean years.

"Dr. Sachs' latest and greatest contribution to us was in his accepting the position of Chief of the Division of Child Neurology when it was formed in 1935. It was his interest in that service, the personal support he gave to it and the financial support he obtained for it that assured the success and permanency of the Division.

"Fortunately, he has never lost his interest in the Neurological Institute."

From my own personal view point, I wish also to express my admiration and deep affection for Dr. Sachs. I have always found an endless source of unfailing good humor, courtesy, friendliness and helpfulness in Dr. Sachs. He has always been ready to give of his time and patience in straightening out all kinds of tangles. His wisdom in handling difficult situations has been without limits and his advice and counsel have always been at the disposal of his host of friends. He is The Elder Statesman and the Dean of American Neurology.

I and my generation entered Medicine when Neurology was in its Augustan age with Sachs, Starr, Dana, Bailey, Peterson, Jelliffe and others as the bright luminaries here in New York; of all of these, Dr. Sachs alone remains active and I can never see or think of him without being reminded of the Latin quotation, "Si monumentum requiris circumspice"—and you will see Barney Sachs.

Dr. Ira Cohen:

It is said that first impressions are lasting ones. My first impression of Dr. Sachs was some thirty-two years ago in this room. He was at that time an examiner of the candidates for internship. He sat at one end of this table, only on that day the table was much longer. It seemed to me to be at least a block long. I was filled with a feeling of awe, awe based on fear. As time went on and I began to learn a little neurology I was filled with awe at the contributions of Dr. Sachs as a pioneer in the field of neurology. Today it is a feeling of awe at the vigor and the active useful life of an Octogenerian. The speakers this afternoon have tried to paint a picture of Dr. Sachs. But when you consider that it took Dr. Adolf Meyer thirty-seven printed pages in this volume to express his appreciation of the man, you can understand that in the limited time at their disposal the speakers could only show some of the highlights. Dr. Sachs! On behalf of your colleagues and other admirers it is my privilege to present to you this volume, an issue of the Journal of The Mount Sinai Hospital. It represents their esteem and a labor of love on the part of its Editor, Dr. Globus.

Dr. Barney Sachs:

Mr. President, Mr. Chairman, Distinguished Speakers, Colleagues, Friends all—

Unintentionally you have put me on the spot. For more than fifty-five years, I have been preaching emotional self control and today you want me to show whether I can practice what I preach. I confess I am a bit disturbed by what my good friends have said about me. I am not, however, going to enter upon any controversy although I feel there is some exaggeration in the picture as presented. Let me seek refuge from my dilemma by recalling the pleasant associations I formed in this hospital during that long period of active work from 1893 to 1924.

I recall with great satisfaction the Presidents of the Hospital: Mr. I. Wallach, Mr. George Blumenthal and Mr. Leo Arnstein. For the most part, although there may have been a few rubs, the relation between the Medical Board, of which I was Chairman for a number of years, and the Trustees was amicable.

After all, both the laymen and the medical men were devoted to the best interests of the patients and the hospital. I was fortunate in joining the distinguished men on the Medical Board in the early nineties. Let me recall the names of Abraham Jacobi, E. G. Janeway, Rudisch, Fluhrer, Gruening, and above all, my life-long friend, the great surgeon, Arpad Gerster, who favored me, young as I was, urged my appointment and enabled me as neurologist to assist him in the capacity of clinician in the pioneer work done in brain surgery. We were among the first in this city to attempt to cure epilepsy by surgical means and to remove brain tumors; and mind you, this was long before neuro-surgery was the American specialty.

This was before Cushing, Dandy, Frazier of Philadelphia, Elsberg, Ernest Sachs and many others had established neuro-surgery as the great specialty it is this day.

I recognize what these men have done of late years but I feel it only fair to state that the great general surgeons of the last third of the last century paved the way for the great accomplishments of later years and I am very happy to recall that just a little later, a general surgeon of this hospital, A. A. Berg, performed one of the most successful operations on a tumor of the Gasserian Ganglion which I referred to him.

I am certain that Dr. Ira Cohen, prominent neuro-surgeon of today, will sympathize with me in recognizing the merits of the older men.

When Dr. Globus and his committee undertook the arduous task of organizing today's function, I had one misgiving. At this period it seemed unfair that so much effort should be expended on any one individual when I know that our effort and our devotions should be and are directed to the welfare of the Nation, the State and the Community. After all, we are living in a glorious country in which research in medical science is and will remain entirely unfettered. It is a source of special pride that I have contributed my mite to the progress of American medicine.

Referring to my medical activities, I wish it were "the end of the beginning" and not the other way around. However, my younger associates will allow that I still seem to have some problems up my sleeve and I hope with their aid, even at this late day, to attempt the solution.

To all my colleagues, let me say what they may have heard before—"The joy of work is the joy of life." To those who have grown old with me, I say, do not let the Biblical three score years and ten affect you—"To add to the years, stop counting them."

May I ask the Chairman of the Medical Board to tell the members of the Neuro-Psychiatric staff that I envy them the great opportunity they have as never before, to contribute to the further development of their specialty in this new era of electrical and chemical research into the activities of the brain and nervous system. And above all, let all your work at Mount Sinai, as in the other hospitals, redound to the glory of American Medicine.

*The Story of The Mount Sinai Hospital, of which the first six installments appeared in preceding numbers of the Journal, is offered in celebration of the Hospital's ninetieth birthday. In its present form it consists mainly of brief historical notations which to some extent reflect the "way" of medicine, in New York and elsewhere, as well as the changing environment since 1852. It has been compiled by Miss Jane Benedict from Hospital records, correspondence, medical and historical literature, and interviews with those who have been both eye-witnesses of and contributors to the Hospital's progress. It is presented mainly as source material from which later a more complete history of the Hospital is to be written.**

The Jews' Hospital in New York was incorporated in 1852 by a group of public-spirited citizens, and in 1855 the doors of its first building on West Twenty-eighth Street were opened to receive patients. Staffed by some of the most prominent physicians of the day, the institution soon proved itself an excellent testing ground for the new methods and techniques which were being introduced into the rapidly broadening practice of medicine and surgery. During the Boyne Day riots, the cholera epidemic, and the Civil War, the Hospital showed its readiness to serve in time of crisis. In 1866 it was given its present name, The Mount Sinai Hospital. By this time it was outgrowing its first home, and in 1872 moved to larger quarters at Lexington Avenue and Sixty-sixth Street.

The present installment describes the expansion in organization that paralleled the growth in size and in medical resources, the formal establishment of the Medical Board and the Dispensary for treating "Out-Door" patients, the enlargement of the House Staff, and the separation of Medical and Surgical Services.

GROWTH AND DEVELOPMENT, 1870–1904

VII

During the years Mount Sinai spent in its Lexington Avenue building, 1872–1904, medical events of great significance were occurring throughout the world. During that period Louis Pasteur taught chemistry at the Sorbonne, and from 1889 until his death in 1895 directed the work of the Institute which bears his name. Robert Koch, co-founder with Pasteur of the science of Bacteriology, announced his discoveries of the bacilli of anthrax, of tuberculosis, and of the dread cholera. The infective agents of leprosy, gonorrhea, typhoid fever, lobar pneumonia, and diphtheria were found at that time.[25]

These epoch-making discoveries in Europe awakened in the United States the realization of the necessity of scientific research in medicine and despite the lack of centers for concentrated research significant contributions to American medicine had been made in the first half of the nineteenth century. The medical societies, the medical colleges and the academies of medicine, the most important

* Corrections, if errors of fact or interpretation are discovered, and additional information which may help to make the picture more complete are welcome and may be addressed to the Historian of the Hospital.

[25] Garrison, Fielding H.: History of Medicine, W. B. Saunders & Co., 1924.

of which was in New York, and such organizations as the Pathological Society of Philadelphia which Silas Weir Mitchell had helped to found in 1857, all made their modest contributions to medical research.

The first American publication of comprehensive research did not appear until late in the nineteenth century. The volumes of *The Medical and Surgical History of the War of the Rebellion*, compiled in the office of the Surgeon General of the United States, were issued one by one in the years between 1870 and 1883.[25] Although the first physiological laboratory in the United States had been established in 1871,[25] it was not until 1886 that the first center for organized research was founded with the opening of the Pathological Institute at Johns Hopkins University Medical School, under the leadership of William Henry Welch. This was the first step made by America in the march of scientific medicine.[26] Seven years later Mount Sinai set aside a small room for its laboratory and the men who formed its Staff played a part in this chronicle of medical progress.

With the prospect of moving into a larger building and caring for a greater number of patients, the Medical Staff of The Mount Sinai Hospital met in January of 1872 at the home of Willard Parker, Consulting Surgeon to the Hospital, to consider improvements in the Hospital's organization and the work of its professional staff. The meeting was called to order by the great surgeon, whose impressive stature was tempered by a face expressing kindliness and good humor.[27] The minutes of that meeting record that "Dr. Parker was chosen Chairman and Dr. Percy was chosen Secretary for the ensuing year."[28] The latter, an Attending Physician to the Hospital, was born in England, had received his medical degree at the College of Physicians and Surgeons in New York, and had been one of the founders of the New York Academy of Medicine in 1847.[29] Also present at that meeting was the other Consulting Surgeon, Thomas Markoe. Like Willard Parker, Markoe had served on the Staff since the Hospital's first year of service. There were three Attending Surgeons, Krackowitzer, Raphael, and Guleke. Ernst Krackowitzer was a tall, wiry man of whom it was said, ". . . he had an open and straightforward character, was an indefatigable worker, a kind and unselfish colleague . . . he was active in every worthy movement."[15] Benjamin Raphael was in that year Mount Sinai's delegate with Abraham Jacobi to the convention of the American Medical Association in Philadelphia.[30] Herman Guleke, a graduate of Dorpat, "had a good equipment of medical knowledge."[15] There were four Attending Physicians on the Staff: Abraham Jacobi, already a recognized leader in the field of pediatrics; Ernest Schilling, who did not live to see the Hospital move into its new quarters; Samuel Percy;

[26] Sigerist, Henry E.: American Medicine, W. W. Norton & Co., 1934.

[27] Ruhrah, John: Willard Parker, Annals Med. History, New Series, Rep., Vol. 5, Nos. 3, 4, 5.

[28] Minutes of Medical Board Meetings, The Mount Sinai Hospital, January 11, 1872.

[29] Notes on List of Founders of New York Academy of Medicine, Dr. Samuel Purple. In possession of New York Academy of Medicine.

[30] Minutes of Medical Board Meetings, The Mount Sinai Hospital, May 5, 1872.

and Charles A. Budd, who had persuaded Dr. Jacobi to join him on the faculty of the New York Medical College,[31] where in 1862 the latter established the clinic which initiated bedside teaching in pediatrics.[32]

At this meeting it was resolved "That the Board of Directors be notified that the Medical Staff of The Mount Sinai Hospital have organized for the consideration of all matters appertaining to the Medical Management of the Hospital." The term had been loosely used before but this marked the actual organization of the Medical Board.

At the first Medical Board meeting a plan was discussed which was to develop into the creation of the House Staff. For twelve of the years the Hospital had spent on Twenty-eighth Street, Dr. Seligman Teller had faithfully served as House Physician and Surgeon, thus caring for both branches of the service at the same time. When the removal of the Hospital to Sixty-sixth Street was announced Dr. Teller tendered his resignation because his practice, which he had apparently carried on while he held his position at the Hospital, was located in the lower part of the city.[33] According to the minutes of that meeting, "It was thought by all that at the opening of the new Hospital at least two Assistant Physicians and Surgeons would be needed and that gentlemen well qualified to act as Assistants could be obtained, in fact would apply for the position."[28] It was further decided that " . . . an examining board of Drs. Krackowitzer, Jacobi, and Percy be appointed for the year 1872, which board will receive applications for vacancies and examine candidates for the position of House Physician."[28] The Secretary recorded that " . . . he would tomorrow take the proper steps to put notices on the blackboards of all the Medical Colleges in the City for application."[28]

During the first five years of the Hospital's occupancy of its new building, considerable difficulty was encountered in maintaining a staff of two House Physicians and Surgeons, a situation due partly to the failure of many applicants to pass the examination. One inventive young man succeeded in dodging the examinations for three months, meanwhile insisting that he was a graduate of the University of Paris but that his diploma had been burned in the Chicago fire. At the end of three months his diploma was proved to be as fictitious as his excuses.[34]

Not without significance is the fact that in the first year the new plan was undertaken, one of the applicants was a woman, Ann A. Angell. She was accompanied by Eliza Phelps who took an examination for Apothecary. Both these women, graduates of the Woman's Medical College of the New York Infirmary, stood highest in their respective examinations. In those days it was considered highly unusual for a woman to enter the medical profession. The Medical Board recommended the two applicants to the Board of Directors,

[31] Collectanea Jacobi, Vol. 1, Introduction, Critic and Guide Co., 1909.

[32] Garrison, Fielding H.: Dr. Abraham Jacobi, Reprint Science, N.S., Vol. 1, No. 1283, 1919.

[33] Interview with Miss Lillie Guinzburg, Niece of Dr. Seligman Teller, June 30, 1938.

[34] Minutes of Medical Board Meetings, The Mount Sinai Hospital, April 30, 1873.

but were told that " . . . the Board did not receive the nomination of women very favorably." The Medical Board, however, had been so well impressed that Dr. Percy was sent to a Directors' meeting to urge the appointments of Drs. Angell and Phelps. The Board of Directors finally conceded and appointed Dr. Phelps Apothecary and Dr. Angell Second Assistant instead of First. As such she was to care for female patients only, except in emergencies.[35] Such an emergency arose in 1873 when she acted as Temporary House Physician and Surgeon. As no other Assistant was available at the time, the Attending Physician, Dr. Percy, called daily at the Hospital to help her in her tasks.[36] The Board of Directors apparently repented of their previous attitude, and in

Dr. Mary Putnam Jacobi

that same year sent three hundred dollars to Dr. Angell "as an acknowledgement of her valuable services during her stay in the institution."[37]

The month before the Hospital moved from Twenty-eighth Street, Dr. Jacobi introduced a resolution at a meeting of the Medical Board to "establish an out-door department to the Hospital."[38] The suggestion was approved by the Directors who announced in the Annual Report of 1872 that besides anticipating

[35] Minutes of Medical Board Meetings, The Mount Sinai Hospital, November 10 and 17, 1872.

[36] Minutes of Medical Board Meetings, The Mount Sinai Hospital, June 12, 1873.

[37] Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, May 11, 1883.

[38] Minutes of Medical Board Meetings, The Mount Sinai Hospital, April 30, 1872.

". . . opening an Infirmary for the treatment of out-door patients," they intended " . . . greatly to extend the sphere of its (the Hospital's) usefulness by the establishment of a clinique, contributing thereby to the advancement of medical science and aiding the student in the study of his profession."

Ever since the earliest days of the Hospital's existence, men and women who were not ill enough to be hospitalized had come to be treated by the House Physician and Surgeon. But with a growing number of patients and a larger institution it was necessary to provide a more satisfactory arrangement. Although a Dispensary was mentioned as an accomplished fact in 1874 it was not until 1875 that the plan of three years earlier was fully realized and a separate Dispensary Staff was appointed.[39] In that year, four divisions of the Dispensary or "Out-Door" (today Out-Patient) Department were established: Internal (Medical), Surgical, Gynecological, and Children's. All these divisions occupied two small rooms in the basement of the building. By the end of two years four rooms were provided. Today Mount Sinai's Out-Patient Department is housed in its own special building with the Children's Clinics held in another building. The total number of clinics, both adult and children's, has now reached seventy. The Dispensary though small in 1875, soon was recognized as being of great educational value, and the division of Dispensary work served as an early sign of the Hospital's participation in the trend toward specialization.

The Dispensary Staff consisted of eight Physicians who elected a President and Secretary, and held regular meetings. At the head of the Gynecological Department was Paul Fortunatus Mundé, editor of the *American Journal of Obstetrics*. He was a regal figure with a fine head, long sweeping mustache, massive shoulders, and a military bearing.[40] Gentle with his patients, popular with his colleagues, a born raconteur, his was a colorful personality. He had come to the United States at the age of three with his father who had fled from Germany after the Revolution of 1848.[41] He was brought up in Massachusetts and entered Yale Medical School, but left to join the Union Army at the outbreak of the Civil War. He was then only seventeen. Later he entered Harvard Medical School, graduating in 1866, and then returned to Germany where he spent seven years. As a volunteer in the Bavarian Army, Dr. Mundé served as assistant surgeon during the Austro-Prussian War and later as battalion surgeon in the Franco-Prussian War. Afterwards he studied gynecology and obstetrics in Heidelberg, Berlin, and Vienna.[42] In his capacity of first head of The Mount Sinai Dispensary's Gynecological Department, he attracted to it much clinical material.

The Children's Department was placed under the leadership of Mary Putnam Jacobi, another sign of the Hospital's early progressive stand on the appointment of women. Mary Jacobi (then Mary Putnam) was the first woman to graduate

[39] Minutes of Board of Directors' Meetings, The Mount Sinai Hospital, February 21, 1875.

[40] Interview with Dr. Howard Lilienthal, April 5, 1939.

[41] Jacobi, Abraham: Portrait of Dr. Paul Fortunatus Mundé, New York Medical Journal, November 10, 1906.

[42] Mann, Matthew D.: Paul F. Mundé, American Journal of Obstetrics, April, 1902.

from the New York College of Pharmacy,[43] and the sixth woman to graduate from any American medical college.[25] In 1864 she had gone to the Female Medical College in Pennsylvania. So impressed was the College with her training that she was granted a degree after "a brief course" of only one year. But apparently Mary Putnam was less impressed than her alma mater and, after some experience gained at the New England Hospital, she dared to seek admission to the awe-inspiring École de Médicine in Paris, the first woman to do so. Such

Dr. Paul F. Mundé

a step required courage in those days, when to enter a classroom full of men was to take one's seat amidst hostile and often vocal disapproval, not only by the students, but also by the professors. So apprehensive were the authorities at L'École de Médicine that they advised Mary Putnam to wear men's clothing in order not to attract attention to herself! She was wise enough to refuse. She returned to the United States in 1871, an accredited graduate of L'École, and immediately became active in her profession. Through the influence of Abraham

[43] Robinson, Victor: Abraham Jacobi, Medical Life, Jacobi Number, Vol. 35, No. 5, May 1928.

Jacobi, whom she met on her return to this country, she was accepted as a member of the New York Academy of Medicine. In 1875 she and Abraham Jacobi were married.[43]

James J. Walsh has written, "After the Blackwells (pioneers in the struggle of women to gain medical education) the most important factor in the movement that brought about the introduction of medical education for women, and probably to be considered after them only in time, for her professional influence was coordinate with theirs, was Mary Putnam Jacobi."[44]

One of the important trends in nineteenth century medicine was the rapid advance made in surgery. In the United States however the Listerian methods, fundamentally responsible for such progress, were slow to take hold, and surgery of the seventies and eighties still reflected the practice of an earlier day. It was not until 1877, in the Presidency of Adolph Hallgarten, that Mount Sinai set up two distinct services, Surgical and Medical, with separate wards for each. Before that, although the division of surgical and medical cases had, of course, been recognized by the members of the Staff, the only division of patients in the wards had been on the basis of sex. Previous failure to separate the services was due to the fact that in those days surgery was hardly considered a separate practice. The situation in 1874 was such that " . . . without exception, the visiting (attending) surgeons of all New York hospitals were general practitioners first, and surgeons in an accessory way. No one was a surgeon as we understand the term now, hence any one might be a surgeon if he chose to operate and found patients willing to submit."[15] Surgery was considered a branch of medicine to which doctors turned only as a desperate remedy, since they " . . . in a general way considered surgical interference an extremely risky and doubtful expedient. Up to the eighties, or thereabouts, no one could have supported himself by the exclusive practice of surgery; there was not enough of it."[15]

The most common operative procedures were of an emergency nature, for relief of strangulated hernia, and for relieving suffocation by tracheotomy. Consultations were the order of the day, before even a relatively minor operation. As many as six doctors might consult. Each stated his opinion, starting with the youngest, and the majority ruled. The prevailing fear of surgery is more easily understood when it is realized that the rules of antiseptic procedure were not generally observed. Infection caused a high mortality rate, as much as 35 per cent in the case of amputation. Yet Joseph Lister had used carbolic acid as an antiseptic in 1865 and his methods had made sufficient headway in Europe so that in 1872 it could be written of Volkmann's Clinic in Halle that there was " . . . the strict application of the new Listerian method of wound treatment," and that "scrupulous cleanliness and liberal use of the carbolic spray and solution were the rule. The results were marvelous, and incomparably superior to anything ever seen before."[15] But it was not until 1878 that an amputation according to Listerian methods was performed in New York. The operator was Arpad Gerster, who in 1880 was appointed a member of the Attending Staff at Mount Sinai.

[43] Walsh, James J.: History of Medicine in New York, National Americana Society, Vol. 1, 1919.

To be continued

ABSTRACTS

Authors' Abstracts of Papers Published Elsewhere by Members of The Mount Sinai Hospital Staff

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

Extreme Eosinophilia and Leucocytosis. M. H. Bass. Am. J. Dis. Child. 62: 68, July 1941.

An unusual syndrome characterized by persistent, very marked eosinophilia and leucocytosis with general adenopathy and, in some cases, mild splenomegaly is described. Three cases are reported. One child died from intercurrent disease. The second recovered after eight years of observation. The third patient was observed from the onset of the illness which was accompanied by low grade fever, eosinophilia of 83 per cent and leucocytosis as high as 53,000 white cells. This child who has been followed for two years is recovering. The pathogenesis of these cases is discussed, especially their relation to leukemia; the usual causes of eosinophilia having been excluded, it is believed that this condition is some form of chronic infection. The prognosis is apparently good.

Dietetic and Related Studies in Multiple Sclerosis. R. M. Brickner and N. Q. Brill. Arch. Neurol. & Psychiat. 46: 16, July 1941.

An investigation was made of the lifelong dietary habits of 34 patients with multiple sclerosis. In general, patients with multiple sclerosis are poor eaters, the consumption of visible fat, particularly of dairy fat, being especially poor. In 17 patients (group 1) these defects were quite obvious. In 5 others (group 2) the material gave ground for strong suspicion that the defects existed. In 8 (group 3) there were suggestive, but uncertain, evidence, and in 4 (group 4) there were no signs of abnormality. Various theoretical aspects derived from these observations are discussed.

Sustained Hypertension Following Unilateral Renal Injuries and Effects of Nephrectomy. B. Friedman, J. Jarman, and P. Klemperer. Am. J. M. Sc. 202: 20, July 1941.

Sustained hypertension was produced in rats by means of an injury to one kidney, the opposite kidney remaining intact. Removal of the injured kidney resulted in a decline in blood pressure not to the prehypertensive level but to some point above it depending upon the severity of the hypertension. Hyalinized and necrotic vascular lesions were observed in the intestines, pancreas, heart and unoperated kidney in some animals. Their presence was associated with rapidly rising severe hypertension, but not necessarily with nitrogen retention.

Maintenance of an elevated pressure long after the removal of the injured kidney of a hypertensive animal suggests that irreversible changes have occurred which may possibly be related to alterations in the vessels.

Causes of Painless Gastro-Duodenal Hemorrhage. E. Moschcowitz, S. Mage, and V. H. Kugel. Am. J. M. Sc. 1: 52, July 1941.

Painless gastro-duodenal bleeding is usually the result of erosions and duodenitis; less frequent are true callous peptic ulcers. In one of our 14 cases no cause could be found. In painless gastro-duodenal hemorrhage where roentgen-ray evidence of peptic ulcer is absent or inconclusive, further study of the patient is obligatory to determine the cause of the bleeding. The genetic relation of gastro-duodenal erosions to peptic ulcer is discussed. In the light of our current knowledge it is impossible to insist upon a unitary origin of gastric erosion or upon its invariable genetic relation to callous peptic ulcer.

Total Cystectomy With Bilateral Nephrostomy for Carcinoma of Bladder. A. Hyman. Ann. Surg. 114: 149, July 1941.

A male patient aged fifty-one was admitted to the hospital in August, 1934, with a five year history of hematuria, dysuria, loss of weight and fever. Cystoscopy and cystograms demonstrated a huge vesical neoplasm; the biopsy revealed an infiltrating squamous cell carcinoma. Because of an infected right kidney, a nephrostomy was first performed, this was followed by a left nephrostomy and total cystectomy. Within six months after operation the patient gained forty pounds in weight and his hemoglobin rose from 35 per cent to 70 per cent (Sahli). Now, five years later, he is in good condition, with no evidence of recurrence or metastases.

Immunity to Tetanus Induced by Combined Alum-Precipitated Diphtheria and Tetanus Toxoids: Based on a Study of 186 Allergic Children. M. M. Peshkin. Am. J. Dis. Child. 62: 9, July 1941.

A preparation of combined alum-precipitated toxoids was injected subcutaneously in two doses of 0.5 cc. each at intervals of from one to ten months. Local reactions were harmless. No general reactions, such as urticaria or asthma, occurred. The results show that the development of active immunity against tetanus was influenced by the age of the patient and the interval between injections.

The results obtained in this study suggest that to insure adequate protection against tetanus for all children treated, three doses (of 0.5 cc. each) of alum-precipitated toxoid should be administered at intervals of at least one month. Furthermore, it is recommended that at the time of an injury a "stimulating" dose of alum-precipitated tetanus toxoid should be given. Finally, should exposure to tetanus occur before vaccination is completed and immunity established (7 to 30 days) a simultaneous injection of antitetanus serum and toxoid (serovaccination) should be given.

A Technique for the More Precise Localization of Pulmonary Abscesses. C. B. Rabin. Am. J. Roentgenol. 46: 1, July 1941.

The method consists of the injection, under fluoroscopic control, of a mixture of 0.2 cc. each of iodized oil and 1/2 per cent methylene blue into the intercostal muscle over the approximate site of the abscess. Roentgen-ray examination is repeated and the relationship between the injected material and the center of the abscess is determined. By exposing the injected blue material at operation and utilizing the information gained from the roentgen examination, the abscess is readily located.

Congenital Anomaly: Rotation of the Kidney. G. D. Oppenheimer, and B. S. Wolf. J. Urol. 46: 17, July 1941.

An uncommon anomaly of rotation of the kidney, namely excessive dorsal rotation, is described; very few similar cases have been recorded. The unsuspected rotation was found at operation for calculous disease. The ureter descended from the mid-portion of the anatomic lateral border of the kidney. In other words, the hilus, with the vessels coming from a posterior position, was found situated in a lateral position. The pathogenesis, the varieties, diagnosis and importance of congenital abnormal renal rotation are discussed.

Filing System for a Teaching Collection in Roentgen Diagnosis. M. L. Sussman. Am. J. Roentgenol. 46: 109, July 1941.

The system has many advantages. It is flexible; use of the "library system" permits subheadings to be inserted or dropped without any disturbance of the main system. The "break-down" of minuteness of subdivision can be as great or as small as is needed. Since the library system demands filing by numerical sequence, only as many guide cards need to be used as are required for rapid numerical localization. This depends only on the number of envelopes and not on the number of disease headings. For example, if the esophageal lesions are few, they could be filed in the numerical sequence of their code designations behind one guide card, 71.0. However, many guide cards such as 71.1, 71.3, etc.,

could be used as the file becomes larger in that particular section. A clerical worker with no medical vocabulary can locate any desired examples of disease in the files; the same lay person can reinsert them.

Colonic Spasm as Cause of Intestinal Obstruction. R. Colp. Surgery, 10: 270, August 1941.

Colonic spasm of sufficient intensity to produce intestinal obstruction is rare but does occur. The exact cause of the spasm is not often obvious but may be due to: 1) stimuli acting at the site of the spasm; 2) stimuli arising from distant foci; 3) stimuli arising or acting through the central nervous system.

The contracted area may extend from the caecum to the rectosigmoid, or may involve only a small segment of bowel. Proximal to the obstructed portion, the colon and even the small bowel is dilated. The contracted area may disappear under anesthesia at the time of laparotomy.

Treatment may be conservative if spasm is recognized as the cause of obstruction. Operative decompression, i.e., cecostomy or colostomy, become necessary if the obstruction is marked. It is important to repeat the colon x-ray examination after preliminary operative decompression, as the cause of the obstruction may be spasm and the secondary laparotomy will thus be avoided.

Problem of Carcinoma of Cardiac End of the Stomach. J. H. Garlock. Surg. Gynec. & Obst. 73: 244, August 1941.

The author reports a series of 15 cases of adenocarcinoma of the cardiac end of the stomach that were explored. In 33.3 per cent the tumors were operable. There was no operative mortality in the inoperable group. Five patients were subjected to radical resection with intrathoracic esophagogastrostomy. Two patients succumbed after the operation; one of a cerebral hemorrhage and the other of inanition and old age. Of the remaining three patients, one is alive one year after operation but with evidence of local recurrence; one is alive and well five months after operation, and the third is well four and one-half months after operation. The author believes that if a patient with an operable cancer of the cardiac end of the stomach a 60 per cent chance of surviving an attempt at radical removal can be offered, the risk should always be undertaken.

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The (*) preceding the page number indicates an original article; the letters "ab" similarly placed indicate an abstract; "cp" signifies a clinical-pathological conference report; "cnp", a clinical neuropathological conference report. Author entries are made only for original articles.

Sigismund Schultz Goldwater

February 7, 1873-October 22, 1942

Resolutions and Appreciations

RESOLUTIONS*

Whereas, The people of the City of New York have learned with sorrow of the death of Sigismund S. Goldwater; and

Whereas, Dr. Goldwater was a native New Yorker whose training and experience in his sphere of endeavor was gained amongst us here in the City of New York; and

Whereas, Dr. Goldwater has been proclaimed both by the architectural and medical profession as an outstanding expert in the fields of hospital construction and hospital administration, and as such had assisted in the planning, construction and operation of hospitals all over the world; and

Whereas, Dr. Goldwater served the people of the City of New York during the years 1914 and 1915 as their Commissioner of Health under the Honorable John Purroy Mitchel, Mayor, and also as their Commissioner of Hospitals from 1934 to 1940 under the Honorable Fiorello H. La Guardia, Mayor; and

Whereas, His other undertakings, achievements, titles, awards and distinctions are not only too numerous but too well known to mention here; therefore be it

Resolved, By this Council in meeting duly assembled, that it is fitting for them to note the passing of Sigismund S. Goldwater, one of our City's outstanding citizens, and that they extend its sympathy to his widow, Mrs. Clara A. Goldwater; and be it further

Resolved, That as an additional mark of respect, when this Council adjourns, it does so out of respect to the memory of Sigismund S. Goldwater.

*Resolution presented by Mrs. Earle and adopted by the Council of the City of New York November 5, 1942.

The death of **Sigismund S. Goldwater** comes to the Board of Trustees of The Mount Sinai Hospital as a stunning blow. Since his first association with the institution more than forty years ago, he has occupied a place in our affections which has been accorded to few men. As Intern, Assistant Director, Director and Trustee, he won our admiration and endeared himself to one and all.

The position that he occupied in the health and hospital fields was quite unique and both as planner and administrator of hospitals he had won national and international fame.

He served as Health Commissioner and Commissioner of Hospitals for the City of New York and under his magic touch these departments flourished and developed.

We shall sorely miss his vision, his keen mind, and above all his lovable personality.

As a mark of respect the flag of the Hospital has been placed at half staff, and to his bereaved wife and to the other members of his family is extended this expression of deepest sympathy upon their irreparable loss.

Leo Arnstein, *President*
George Lee, *Acting Secretary*

* * *

The Medical Board of The Mount Sinai Hospital mourns the passing of **Dr. Sigismund S. Goldwater.** The Hospital has lost a wise councilor and friend who as Medical Director and then as Trustee served the Hospital for over forty years. During these years he exerted a guiding and constructive influence on the development of the Hospital.

Ira Cohen, M.D., *President*
Marcy L. Sussman, M.D., *Secretary*

* * *

The Association of the Junior Medical Staff of The Mount Sinai Hospital extends its sincere sympathy to the family of **Dr. Sigismund S. Goldwater.** The Association mourns the loss of this most distinguished physician-administrator and medical executive whose accomplishments assure him a lasting memory.

Samuel H. Averbuck, M.D., *Vice-Chairman*
Solomon Silver, M.D., *Secretary*

* * *

The Associated Alumni of The Mount Sinai Hospital have learned with sorrow of the death of **Dr. Sigismund S. Goldwater.** We extend our profound sympathy to his family and feel deeply the loss of a wise councilor and a devoted friend.

Harry Weiss, M.D., *President*
Elmer S. Gais, M.D., *Secretary*

APPRECIATIONS

I*

I have been asked by the friends and lifelong associates of Sigismund S. Goldwater to speak a few words in their behalf at this sad parting. Words fail me and I feel quite inadequate. Those of us who shared the privilege of his friendship and the long years of association with him are most grateful for the opportunity we have had. The opportunities that he has given us in our daily work, our esteem and admiration, cannot be measured in words. We have lived side by side with him and witnessed the unfolding panorama of a great life.

His entire career from its very beginning was characteristic of the man. Unfaltering in his vision, with his eyes set upon the distant goal of public service, following a short career in business, he sought for broader fields of opportunity to serve the people. He created a new field of medical work.

Fortunately, he was gifted technically, personally, and in an administrative way, and fortunately, at the outset of his career, the right opportunity to exercise his talents was presented in the institution with which he was associated, The Mount Sinai Hospital. He broadened its scope and developed it both functionally and physically, into a great institution which led the vanguard of hospital progress in the medical world, and following the trail which he blazed, institutions throughout this entire country and throughout the world were stimulated to follow the pattern which he had set.

Just as Dr. William H. Welsh was responsible for founding the great professional field of public health, so he was the founder of modern hospital administration in this country. His influence upon institutions was a personal as well as a directive one, as is exemplified by the fact that he was consultant to more than 150 great hospitals. His influence extended to foreign lands—to China, under the auspices of the Rockefeller Foundation, to Central and South America, and even to Russia under the Soviet regime.

We shall never know how much we owe to him personally, nor how much the world owes to him. We know that he has made for us a rich opportunity for public service to which all of us must devote our lives.

Following a distinguished career in hospital administration, he was called upon in the first Mitchel administration of this city to create a new Health Department. Because it may not be well known, I should like to place on record here and now, that not only did he create a modern Health

* Delivered at the funeral services conducted at the Ethical Culture Society Meeting House, October 24, 1942.

Department to serve the people of this city, but it was his vision that first foresaw the need and proposed the districting of the city into health districts so that health could be brought down to the people. This idea of his forms today the basis of modern progress in public health. His great municipal plan of health administration has finally been brought to achievement in recent years in this city and in many other cities throughout the land.

Nine years ago, he was again called to be Commissioner of Health in this city, with the idea that he would carry to completion the ideas which he had annunciated in previous years. But as Mr. Morris can tell you better than I, the Mayor realized within a few days that there was a greater mission for him in this city. An enormous hospital system had to be completely rehabilitated, its professional staffs reorganized, its structures improved after many years of neglect. Only he was big enough to take over the 27 gigantic institutions of this city, and, within an incredibly short time, remodel them into the great hospital system which is now the pride of this city and of the nation. Nothing comparable exists in any other city of the world.

The City of New York will ever be in his debt, but the medical profession of New York must never forget what he has done for them in creating the tools with which they carry on their daily work. They must never forget the standards of professional service, which he above all his predecessors in the hospital field instilled into the medical profession and into the nursing activities of this great city.

His entire career was unfaltering—a devotion to an ideal of service to the people; and so, after achieving his objectives in the Hospital Department of the City of New York, he was impatient to move on to still broader fields of public service.

As President of Associated Hospital Service, he succeeded within one year in establishing it on a firm financial foundation, as one step in a plan to save the voluntary hospitals of the city by broadening the base of their public support. Then, moving on into fields which claimed his deepest interest—service to the poor—he conceived and developed the Community Medical Care service. The times were not ripe to bring this to full accomplishment within the short period which remained to him, but the idea—the basic principles behind it, of service to the people while maintaining at the same time the operating standards of hospital and professional work—will flower in the future.

The world must realize that we have lost one of the greatest medical statesmen of these and all times. We, his friends and associates, who held him in high esteem, have lost a dear friend. To the very end of his life he had that youthful resilience which characterized him. His courage,

his energy, the excitement of his planning and of his broad vision was a stimulus to all of us. It was a privilege to be close to him. Although esteem and admiration humbled us in his presence, we formed a close attachment to him and an affection which we shall never outlive.

The great loss which his dear family have suffered personally, they must remember, is magnified by the greater loss to mankind, and to the City of New York, and to the nation. His influence on structures, on organizations, and on people will live after him evermore. We who are assembled here today will earnestly endeavor to carry on his message in our troubled world.

George Baehr

II*

I speak on behalf of the Mayor and the administration of the City of New York. Sitting here in the first few rows are City Commissioners, former colleagues of Dr. Goldwater, who learned to love him. We worked together by day, and we remember him, and always will, as Commissioner of Hospitals of the City of New York, who came into office in a most trying period, when the Hospital Department had reached a very low ebb of service to the people of the City of New York, at a time when the people were scared, when the indigent sick of the City feared to go to a City hospital for care. Dr. Goldwater, during his administration, changed all that, and it was during his years in office that the City of New York's hospital system expanded—more in those few years than in its entire history.

One of his colleagues has given you a sketch of the professional service of Dr. Goldwater, and I need not remind you that under his influence, two of the greatest publicly supported hospitals in the world flourished as they never had before. The standards of care improved in Bellevue and Kings County Hospitals as they never could have, had they not had the benefit of such imagination, such zeal, and such idealism.

I remember him so well, because he was a little bit shy, having been more or less cloistered in professional work, without interference from any opponents. From time to time Dr. Goldwater came down to the City Hall to appear before public bodies for appropriations, and he met opposition. He was often shy and hesitant about fighting back, but he always did. He was always patient, and he always got what he asked for because even his opponents realized he was giving the best that was in him.

Dr. Goldwater gave the early years of his life to The Mount Sinai Hospital, starting as an intern and going to the top of his profession, and then

* Delivered at the funeral services conducted at the Ethical Culture Society Meeting House, October 24, 1942.

he came to the Department of Hospitals of the City of New York, where he spent very harassing years. You all know what those early years were like—from 1934, 1938, and on. Dr. Goldwater was in the midst of what we will always remember as a great reform movement in the City of New York. His accomplishments are a matter of record, and I know that those who mourn his loss will realize that he still lives on in these accomplishments.

All of us are concerned naturally about life and the hereafter. We speculate, we study philosophy, we listen to great speakers, and preachers, but we all have our own ideas of immortality, and even the most cynical of any of the people we know will have to admit that the man who does great work in his lifetime lives on. He lives on in the inspiration which he leaves behind him; he lives on in the work which he started.

Because he was an idealist, Dr. Goldwater knew that his ideals would never be fulfilled. Because he had that capacity of lifting his standards ever higher, he knew, as one year passed into another, that his ideal would expand, always be just out of reach, always tending toward something a little higher. You all know the Latin expression "*altiora pete*" (I learned it in school when I was a boy), which means, always reach a little higher. And that is why Dr. Goldwater was sometimes impatient—because some of the rest of us could not keep up with his ideas. He was impatient with those who could not see as fast or as much as he could. That is why so much was accomplished, and many of his dreams came true—thank God—during his administration.

For Dr. Goldwater the shadows of life have lengthened; the day is over; the evening has come; the busy world is hushed; and his work is done. But our work—those of us with whom he left his inspiration, and his friends, with whom he left another ideal—that work is just beginning.

Dr. Goldwater was not only an idealist, but he was practical, and he knew, as all of us must realize today, that the voluntary hospital system can no longer be supported by a few. Indeed it no longer belongs to a privileged few. The support of the voluntary hospital system must be spread out among the masses, just as music and the arts are being spread out and supported by the masses. So this great service which is rendered for the public must be supported by the public, and that is one of the social problems to which he was devoting the closing years of his life. Most of us thought there were many more years ahead for him to develop that plan and make it work. For those who are left behind, our job is to carry on.

We mourn his loss; we have lost a friend down at the City Hall, and every one of the Commissioners who is here today would like to join me in paying tribute to his memory. Only yesterday it seems he was with us,

and only a few days ago, he was strong and sturdy, as far as we knew. Now he is gone. It seems very difficult for you who knew him well to realize that he is gone. I am sure that every friend of Dr. Goldwater's, particularly in the City Administration, will join me in saying that his work will never cease.

NEWBOLD MORRIS

III*

We are a people who can speak of death quietly, and without fear and honestly. The death of Sigismund Goldwater has brought in his work, in his friendships, in his family, a feeling of irreparable loss.

We pay a price for living. Each of us wants to fill each day with joyousness and work and fulfillment. We want it for ourselves and we want it for those dear ones that we love. This is no longer possible for him, and so it hurts. Life is given and life is taken away.

Even deeper is the pain of parting. As we live we sink our roots into one another. No one liveth to himself alone and no one dieth to himself alone. We pay a price for loving. The more we love and enter into one another's lives, the more the pain. Yet, not to be willing to enter into the lives of others intensively, not to take responsibility and express one's love, because of the fear of the pain that will come with loss, would be cowardly, unworthy of us. And so we have loved him, and we lose him. The pain of that is deep. Yet with dignity and courage we accept this as part of living.

Where shall we find consolation in our loss? We take comfort—great comfort—in the fact that we have been part of his life. If he were to speak, I am sure he would say there should be no note of sorrow, but rather of triumph. He lived a long life, a good life. He has left children who will live on and carry on. He has left monuments in this city, in stone and in the work and health of the people. To have lived on and to have been a burden to himself and to others—this would not have been good. So even in grief we sound a note of gratitude and triumph. We celebrate his life.

Dr. Baehr and Newbold Morris have talked of his work—one representing the Medical profession and the other the City Administration. Yet, I too cannot resist adding a word about Dr. Goldwater's work. And I speak as one of the citizens of the city. When Doctor Goldwater took office, I was working down on the East Side, in the neighborhood of poverty and people in trouble. And the real test of what the people at the top may do—the people at the top in government, and at the top in the

* Delivered at the funeral services conducted at the Ethical Culture Society Meeting House, October 24, 1942.

professions—the real test, is whether their work registers at the bottom—among the people, at the receiving end. And I must tell you that Gouverneur Hospital and Welfare Island Hospital too, as they were when Doctor Goldwater took office, were a disgrace to the people of the city. What rats, what vermin, brutality, hopelessness and impersonal service! But his work, his good work, showed at the bottom. He brought responsibility into the work and it showed in cleanliness, attention to detail, decent, human medical care.

Doctor Goldwater respected individuals for what they were and the way they worked. He respected the autonomy of the boards of the hospitals and the nursing schools of the city. But that did not mean that he accepted *anything*. He had standards and integrity and would not close his eyes to neglect or to mediocre or inadequate service to the people. His creative power showed in the new physical structures like Queens General Hospital and the new Welfare Island Hospital. Beyond his genius at construction was his ability to administer institutions. Above all, his character showed in the way he made appointments—beyond race or religion or nationality; beyond personal loyalties; beyond the foul stench of politics.

To one delegation asking for favors, he said, "There are only two kinds of doctors—good doctors and bad doctors," and he lived that adage. And I say it showed in the work.

For in those '30's, when people the world over were losing faith in the democratic way of life, he did something deeply spiritual. He gave us faith that in a democracy people can come to public service with integrity and efficiency and vision, and dedicate themselves to the public good. He gave us faith in this truth—that good men, able men, can serve the peoples with integrity. In the days when people were saying that democracy was degenerating, he gave us cause to have faith. And that is one of the greatest gifts he gave us.

We may ask, "What animated this man? What was it in him that led him to do this?" He was not the kind of person who attends churches and conforms to the outer practices of religion. Yet he was a deeply religious man, deeply impressed with the mystery of life, deeply reverent. He was especially aware of personality and constantly striving for new insight into the individual. He had a deep sense of the individual. The evidence lay in what he was himself—an aristocrat in his tastes, with a sensitivity to beauty, a dignity and nobility. He was one of the distinctive and distinguished personalities that make the common man uncommonly good.

Many of us who knew him from the public side did not know his deep personal feeling. He was very gifted in music and in language. He wrote verses which had great beauty and imagination, as of a "man walking

among the stars." His humor and wit, the bubbling joyousness, had also a touch of the fun of Gilbert and Sullivan! Many of his profession will recall occasions and ceremonies when his verses were read and relished. There was joyousness beneath his seeming austerity. So always a tenderness so deep, and sensitive, and colorful! To many he seemed shy, distant, stern, politely conforming to the conventions, keeping a distance. But underneath was deep emotion—so deep a feeling and love that it feared its own direct expression. And the way that love showed itself was in the grandest way—not just in demonstrativeness, but in helping people grow. He had the intense personal interest in helping people grow—planning for them from a distance.

When people speak of God and try to say what they mean about God, they begin to talk about beauty in the universe, and order in the universe. But the beauty and order that man hungers for, the beauty and order and goodness which man sees in a supreme reality can be brought about in this world only as it expresses itself in human effort. You and I who speak of God as the God in man, feel the evidence especially in *him*. He cared so much, he longed and hungered so much for beauty, and order, and goodness! He not only hungered for it but brought it into the world in cleanliness and organization and in the relations of people. If there is some power that shapes this world so that man's needs can be met with justice and mercy, it must work itself out through man, through how we live together. And this, a living testimony, he gave through his work and life.

The Jews have said, "Hear, Oh Israel, the Lord thy God, the Lord is one," meaning that we are all of one life in this universe. We owe it to one another to make that life sweet, not bitter. He felt that. And the Christians have said, "I am the resurrection and the life," meaning that there is something in the self that is precious, that is sacred, that is induplicable, and irreplaceable—the wonder, the miracle, the mystery of human personality! And his life was somehow expressed in direction and meaning through those he loved.

Some will remember his public work—of construction and administration and consultation. Some will remember him in connection with both voluntary and government hospital plans. He felt that both forms had a place among free men.

Some will think of him chiefly as a dear friend. We cannot express in words how deeply his wife, his children, and those who call him "brother" will miss him. But, if I may say it, just as it must have been a great joy for him to give love and devotion, the feeling he had of strength, the satisfaction of giving security and support to those he loved, so it must be a great comfort to them through the years to come to know how much that

home meant to him. For through the decades he came to it from the cares, from the dust and dirt, and conflict, into the peace, the patience, the understanding and affection of that home, to renew his body and spirit, to go forth again into the world and do his work. For his loved ones this must be a great satisfaction and comfort and consolation.

There is much in his life from which we can all learn and take inspiration—his sense of the individual, his personal tenderness, his friendship and family, and his vision as a public servant. We leave here, carrying in our memories the beauty of his personality, the effectiveness of his work for a clean city, a healthy people, a better professional standard, a finer citizenship. As comrades dedicated to carrying on his work, and as dear friends who feel his loss, we must take with us also something of his Promethean quality, a godly quality of vision and courage—and, as the poet phrased it:

"To suffer woes which Hope thinks infinite
To forgive wrongs darker than death or night
To defy Power that seems omnipotent
To love and bear
To hope till Hope creates from its
Own wreck the thing it contemplates
Neither to change, nor falter, nor repent;
This is to be good, great and joyous, beautiful and free!
This alone is worthy of thee!
In this alone is victory!"

ALGERNON D. BLACK

WE MOURN OUR LOSS*

Sigismund Schultz Goldwater, M.D. was born on February 7, 1873. During his pilgrimage of three score and ten years, he was our guide, philosopher and friend, stimulating hospital progress in a manner that was unknown before his time. When we spoke of the modern hospital we were conscious of his genius, for no other man has left so many unforgettable memorials in the wards and corridors of our institutions for the sick. Though he is no longer with us, the name that we have conjured with for almost forty years will continue to live as long as hospital scholarship remains to influence our professional lives.

Goldwater was a born public health executive, a gifted leader, a fluent speaker and a facile writer. He administered the affairs of an important hospital brilliantly for a quarter of a century. He was commissioner for a vast public health and a vast municipal hospital organization, on successive occasions, with lasting benefit to his native city. He was the pioneer worker, always in the vanguard, exhorting us with his convincing tongue and pen to follow him. He taught us new, original and better ways of caring for our sick. His versatility was equaled only by his penetrating wisdom and many stood in awe at the sheer power of his intellect. How many that listened to him will ever forget the spell that he cast over them with his presentations, for they combined, in rare quality, the logic and the sentiment which are the prerequisites of hospital progress. Intellectually honest in the highest degree, devoted to the cause of the sick and the poor, he stood high in communal service. His gifts to his readers and to his audiences were given freely and without condescension. Men came away from his presence enriched and refreshed. The crumbs from his table were precious.

Goldwater's touch was golden wherever his energies were brought to bear on problems affecting our hospitals. He led us through dark periods of hospital history, during war and economic depression, and closed his long years of usefulness in this journal by an impassioned appeal for the voluntary hospital and the idea of medical charity for which it stands. The Blue Cross plans which are sweeping our country with their life-saving gifts to hospitals as well as to patients, have special cause to stand in reverence at his bier. The respect which our profession now enjoys in the community is directly traceable to his influence and we remain, therefore, eternally in his debt.

Goldwater was the senior ex-president of the American Hospital Association at the time of his death, and he was also president of the American

* Reprinted from *Hospitals*, November, 1942.

Conference on Hospital Service in his time. The second half of his life was spent in the field of the expert and he proved to be a hospital consultant in the best sense of the word.

Goldwater's final illness, which would have disintegrated a lesser soul, found him as defiant of the angel of death as he had always been in the days when he could help the less fortunate with a lavish hand. He remained cheerful and creative to the end, toying with the light verse which had sustained him in previous dark hours as he regaled his intimates with many choice bits of recent vintage.

Goldwater's life was colorful, and the colors were particularly impressive as sunset closed in on him. Many who had stood by, with deep appreciation for his friendship in the past, prayed for the power of divine intercession which enabled Joshua to command the sun to stand still at Gideon till the battle could be won. He was too precious to lose during these dark days in our nation's history.

Goldwater now takes his honored place in our Hall of Fame. As we close the book, having read the final chapter, we are filled with regret for the end of the sheer enjoyment of reading it. As if it were a volume from the classics, which had just been closed and laid away, we wish that we could have it all over again to read.

Goldwater labored long and ardently among us and has now passed to his eternal rest. May the memory of his noble philanthropy be a comfort and a blessing to us all.

E. M. B.

GOLDWATER*

The magic of his name has held us spellbound for four decades—almost from the day that he asked for and obtained the opportunity at Mount Sinai Hospital, New York, to try his hand at hospital administration. It was an undeveloped specialty in those days and men of mediocre abilities, mostly tired and overaged pensioners of society, had full reign, undisturbed by the march of progress that finally overtook them. The art and science of hospital administration may be said to have been born with Goldwater. He contributed handsomely to its upbringing and left it rich in achievement and promise at the hour of his passing.

Those who were privileged to work in close association with him will take pride in their relationship with this genius of the modern hospital and will talk about it to their children and to their children's children. Few in the history of the hospital have been gifted with as much technical skill and imagination and with as much dynamic power as characterized Goldwater throughout his professional life. He was the guiding spirit in the voluntary hospital principle and was confirmed in his philosophy of medical charity by his intimate experience of seven years with public hospitals. Even those who feel that the sun of the philanthropic hospitals may be setting with Goldwater, just as it rose with him, now stand in homage at his bier.

He had a stimulating and convincing presence which guaranteed successful action in any field that was fortunate enough to win his attention. If it was some new idea that he had not personally initiated, he was at least consulted about it, and his stamp of approval meant that success was assured. His readiness to sense the common need, his keen insight into public health problems, his crystal-clear intelligence and his great ability with the written and the spoken word combined to produce a hospital authority of historic proportions. He was productive in a seemingly effortless way and caused others to produce by his radiant example.

A born New Yorker, he was cosmopolitan and conservative in his tastes, while being liberal in his social, political and economic views. In succession, he was the talented journalist (using stenography till the very end), clinician (an early published monograph on blood pressure from his pen remained in our scientific literature for subsequent quotation), hospital executive and public health administrator. Howard Lilienthal, in his reminiscences, tells of Goldwater's brilliant diagnoses when he appeared to take the practical examinations for internship at The Mount Sinai Hospital. Goldwater's desire for the opportunities of public office was gratified when he was appointed commissioner of health and, years

* Reprinted from *The Modern Hospital*, Vol. 59, No. 5, November, 1942.

later, commissioner of hospitals, leaving a rich legacy of public service to his native city on both occasions.

The honors that came to him from universities, civic organizations, national hospital groups and scientific bodies cast great credit on them and left him unspoiled in the work that he had laid out for himself. Throughout his meteoric career his mind was restless in its search for truth. He was charming and eloquent on the platform and at the festive board. A contribution to the literature of hospital administration from his pen commanded immediate attention. His bibliography is extensive and manysided. A summary of many of his outstanding sentences and paragraphs was published in a recent edition of *The Hospital Yearbook* and read eagerly in this country and abroad.

His colleagues on the editorial board of The Modern Hospital, at the birth of which 29 years ago he stood sponsor, were planning to pay tribute to him in the February issue in honor of his seventieth birthday, but fate took him from our midst. We, therefore, record in these lines our humble tribute to a leader whose star shone brilliantly throughout its course and will continue to cast its beneficent light through many a year to come. He exemplified our finest hospital ideals and this will be a fitting epitaph to mark his place in our memories.

E. M. B.

DR. S. S. GOLDWATER*

"Was it a mere coincidence that Dr. S. S. Goldwater died so shortly after he had written what must have been to him his strongest expression of his convictions that medical and hospital care cannot be regulated effectively and ideally by laws and ordinances, by statute and administrative prescription? The fact, however, that he did die at a time when his mind must have been at a fever heat in the defense of his ideals was, to say the least, a fitting culmination of a life that had been devoted to the procurement of medical and hospital care for under-privileged groups and to the intensive development of such care for all the groups of the population.

"Dr. Goldwater's whole public life was one of mental strife and almost continuous controversy. Remarkable to say, his battles were not defensive; he had learned the tactics that the best defense is a vigorous offense and he waged his battles by battling for his ideal rather than by seeking to destroy the ideal of his adversary.

"The preservation of sound principles in hospital administration and of the adequacies in medical care in our country is due in a large measure to the watchfulness, the shrewdness, and the resourcefulness of Dr. Goldwater. Time and again, as for example, in the controversies arising from the studies of the Committee on the Costs of Medical Care and more recently in the controversies arising from the projected Social Security legislation, he found himself emphatically opposed to students of public policy, sometimes to men of pronounced ability and vigorous conviction. He was able, however, to match his ability and conviction with the ability and conviction of others. It was not always easy to agree with him just as it was never easy to differ from him. His own convictions were so strong that even those who subscribed to them may have had their difficulties in yielding their acquiescence and assent. Sometimes too, his central conviction implied a host of supplemental convictions, and even though one might accept his basic principle, it was not always easy to accept with equal wholeheartedness the implications which he had caused to emerge from his fundamental tenet. For this reason at times even those who stood solidly behind him might have felt that in Dr. Goldwater's mind, he was dealing with adversaries when, as a matter of fact, he was battling his own friendship. Yet with all, he was always sincere, straightforward, honest in the formulation of his views, and unquestionably convincing in their presentation. Hospital administrators throughout the land and beyond will miss his vigorous attack upon hospital problems, his emphatic formulation of his attitudes, his eloquent, and, at times, oratorical appeal for his concept of the right . . . .

* Reprinted in part from *Hospital Progress*, Vol. 23, No. 11, November, 1942.

"The character of the man would well repay the most painstaking analysis. Despite the vigor of his convictions, those with whom he waged controversies remained his friends. He had the rare ability to forget controversies in lending his support even to the very program of those whom he opposed in the development of the program. He saw the interests of the under-privileged groups in public policies and in legislation, even when a less penetrating mind might have overlooked those interests. He had a rare understanding of both the governmental and the private hospital, an understanding which is all the more surprising by reason of the fact that for so many years of his life he himself was a public official in charge of tax-supported institutions.

"The American Hospital Association has lost in Dr. Goldwater one of its strongest supports. He may well be thought of as a foundation personality in that organization, a personality which it will be difficult if not impossible adequately to replace. He had a comprehensive insight into the many projects of the American Hospital Association; he saw and understood the impact of the changing conditions of the times upon hospital matters, yet despite such appreciation, he never lost sight of the unchanging and persistent fundamentals for which he felt he must battle to remain true to himself and his convictions.

"The Catholic Hospital Association gratefully acknowledges many a debt which it owes to Dr. Goldwater especially the debts incurred in the early days of the Association and the debts incurred in these later years when many of the principles for which our Association stands were the very principles for which Dr. Goldwater fought. May his soul, so stirred by the spirit of battle during life, find its victorious peace in death."—

A. M. S., S.J.

DR. SIGISMUND S. GOLDWATER*

The citizens of New York, their government, the sick among them, and all physicians in their private and official relationships have lost by the death of Dr. Goldwater a statesman of the public's health, a designer and administrator of hospitals of world-wide repute, a courageous and independent thinker and author whose life work and influence raised the standards of medical care and its social usefulness to new and high levels.

From the very beginning of his professional career as interne and, soon after, as hospital superintendent, the vigor of his initiative, the soundness and depth of his policies of organization, the swiftness and certainty of his decisions marked Dr. Goldwater for a career in medical administration.

His keen sympathy for persons handicapped by disease, poverty, or social injustice brought him recognition as a citizen of uncommon understanding of the origins of preventable handicaps of men, women and families which society and government together could correct or remove.

His well ordered and disciplined mind expressed itself in the planning and construction of hospitals at the same time efficient for their purpose and beautiful as symbols of a broadening community concept of institutional provision for the sick.

For thirty years Dr. Goldwater was a power for good in the development of the services of government of New York City for the prevention and treatment of disease. No other person has appeared in the field of modern medicine to whom could have been safely trusted in turn the Department of Health and the Department of Hospitals. As Commissioner in the administrations of Mayor Mitchell and Mayor La Guardia, Dr. Goldwater set patterns and ideals of competence, cleared political partisanship out of departmental positions, and enlarged and improved the functions of the departments of Health and Hospitals in a way to bring to himself and his city national acclaim.

Wisdom in public affairs, a sensitive discrimination between matters of first and secondary importance, consideration of the rights of the citizen as well as of the responsibilities of civil government characterized the opinions and actions of Dr. Goldwater as a member of the Board of Health of this City.

We his collaborators and colleagues give this evidence of our sense of sorrow at his death and our thankfulness for the good fortune that gave us his life as an example of the highest type of manhood. H. E.

* Editorial in *Quarterly Bulletin*, Dept. of Health, City of New York, Vol. 10, No. 4, November, 1942.

DOCTOR GOLDWATER*

The most eminent contemporary authority on hospital construction and administration has passed from the scene. He was Dr. S. S. Goldwater, who for forty years devotedly served not only this city but the entire continent. Because of his commanding personality and his zeal he was able to carry into effect policies that might otherwise have remained mere paper ideals.

"The most important person in the hospital is not the governor, the contributor, the doctor, the nurse, the superintendent or the secretary; the most important person beyond all question is the patient," Dr. Goldwater once wrote. The scores of hospitals built in accordance with his advice were designed and conducted not only to make the practice of medicine and surgery more efficient and scientific but with the alleviation of human suffering as the primary consideration. Because he believed in the democratic distribution of medical care, he advocated state regulation, but stoutly resisted that excess of bureaucratic organization which invariably leads to automatism.

After he became the president of the Associated Hospitals Dr. Goldwater saw the necessity of expanding the "three-cents-a-day plan" to include medical care. He also saw the folly of combating private practice before inaugurating a better distribution of medical care. With the practicality of a medical statesman he worked with the local county medical societies. The result was his "community ward plan," which was to make it possible for the white-collar people to obtain the kind of medical service that only a hospital can give. Institutional standardization he accepted only as a momentary state; he insisted that a hospital must constantly grow and improve as medicine advances. He did not live to see all of his reforms carried out into practice, but their momentum is bound to be felt in creating a new type of medical practice with the hospital as its center.

* Editorial in *The New York Times*, Saturday, October 24, 1942.

A SIDELIGHT ON S. S. G.

Joseph Turner, M.D.

No picture of Dr. S. S. Goldwater would be complete without a few strokes of the brush which would reveal the warm and vibrant side of S. S. G., a side which he so well succeeded in hiding from the public eye, but which unquestionably served as a prime source of his will and surge of energy in his devotion to what he considered most useful to the needs of humanity.

The following pages will open to view a few of the many, but not widely known, beautiful traits in the character of this great man—and, above all, will leave a warm glow in the hearts of his many admirers who will thus rediscover in him a loyal friend and the devoted servant of mankind.—Ed.

In his very moving eulogy of Dr. Goldwater, Mr. Algernon D. Black, of the Ethical Culture Society, spoke of Dr. Goldwater's ability to write verse of great beauty and imagination. Not many knew of this gift. It was revealed mostly to a few of his intimates.

This flair for poetry, the setting down of his thoughts in cadence and rhyme, may have stemmed from his unusual feeling for words, their finer nuances, and varieties of usage. Words seemed to have an especial fascination for him; he derived the kind of satisfaction from their study and use as others obtain from music and pictures. Possessed of a very large vocabulary, he seemed to summon words without effort, so that a poem in rhyme or in blank verse would often take shape on paper as fast as he could write it. I have seen some of his verses in their original forms, just as he first wrote them down, and I recall how amazingly few were the corrections and substitutions of second-thought words or phrases.

It was the same ability in the employment of words to convey precise meanings which was apparent in his daily correspondence. His letters were not only a reflection of himself, but also in some magical way of the person to whom he was writing. One who was very close to him for most of his life and saw much of his corresponsence described his letters as follows: "Whatever he wrote bore the impress of his personality. His letters had a unique, individual quality. Even in the routine of his huge daily correspondence he was an artist in the use of language. The bare facts and logical elements were fused into a pattern so that the effect was that of a bit of creative art."

Dr. Goldwater possessed a strong sense of humor and his verses displayed this. If in his official communications he showed evidence at times of terseness and austerity, these qualities were not carried over into his verse. In fact, the real boyishness in him would crop out here—the

same boyishness which he revealed to his intimate friends in moments of play. He showed it when he went abroad on some of his vacations. When still active at the Hospital, he would say that only after he boarded ship to journey to a foreign land could he leave behind the responsibilities of this Hospital. Many of those who met him in London, and Paris, and elsewhere, and who saw him at play, so gay, so joyous and witty, were surprised at this, to them a previously unknown and unrevealed side. On shipboard he would compose a series of humorous limericks on any topic of the hour. A few found their way to me in picture postal-cards mailed during his travels. In these, in good fun, he would compare my sad plight in struggling with the problems at the Hospital in summer heat with his happier circumstance in the cool shade of an English or French cathedral. To my everlasting regret, I cannot find them now; they must have been unwittingly discarded along with many other picture postal greetings received over the years from scores of staff members.

Fortunately, I have saved some of his poems, those which were prompted by various festive occasions. In the intimate circle of his own family, there were many of these celebrations which he would signalize in verse. In the more recent years, when serving as Commissioner of Hospitals, he joined with other City Commissioners at informal parties in which the cares of City administration were put aside. At such gatherings he entertained his official colleagues and the Mayor with these ballads. In his last illness, as in previous slighter indispositions, he made use of his enforced bed rest by writing verse. To my knowledge, he wrote verse for not less than forty years, but the poems that I know best and have saved had their beginnings about ten years ago, when Dr. Goldwater celebrated his sixtieth birthday. For several years, he had been developing and improving his country home at Huntington, Long Island. He had come to love those few acres; they afforded him a long-wanted opportunity to give free rein to his love for growing trees and plants. It was a rather bleak place when he bought it—a Victorian house of many gables, with some early American architectural touches, facing the Sound, with its back to the entrance from the road. A few very old and slowly dying oaks, elms, poplars, and other smaller trees and shrubs were scattered along the sides and rear. They did not present a too pleasing aspect. Standing on the sea wall (which he rebuilt solidly), Dr. Goldwater saw the landscape possibilities of the site and set himself to the task of realizing them. Every summer he would add some new shrubs and bushes—a few at a time here and there—all in keeping with his vision of an ultimate complete and beautiful landscape. He would plant most of them himself and sometimes dig them up later and replant them elsewhere as he would decide upon a better location. The marked improvement which

this brought to his country home was clearly noticeable to all of us who visited him during the twenty summers that he lived there.

On the occasion of his sixtieth birthday, Bluestone, Golub, and I cast about for a special means of celebrating this day, and the thought came to us that nothing we could possibly do would please Dr. Goldwater more than to give him some young trees which would eventually replace the group of old oaks. And so, after a search of nearby nurseries, we found several beautiful pin oaks of fair size and arranged to have these planted at Huntington in the spring of his sixtieth year. Since his birthday was in February, a month when trees could not be planted, we celebrated the day by presenting him with "token" trees at a party at his home, with the assurance that the "tokens" would be replaced by the real trees when he opened his home for the summer.

At the time the choice of the gift of trees was made, I quoted Joyce Kilmer's line, "God alone can make a tree", and this gave Bluestone the happy thought that we should accompany the gift of trees with a verse using Kilmer's line as a beginning. Bluestone wrote the verse and sent it to us for approval and revision; I do not think we added or changed a word.

To

GOLDWATER

on his 60th

"G od alone can make a tree"
O little man that tries to rhyme.

L et now our thoughts in poetry
(D ear to the heart in every clime)
W eave out the rhythm carefully,

A nd sing—How once upon a time
T hree men came all, whose destiny
E ach brought to Sinai. Now the line
R hymes tree with anniversary.

BL

I say that this was a happy thought because we continued this practice in later years and it prompted Dr. Goldwater to reply in kind. The trees were planted in April 1933, and this ceremonial occasion was also celebrated with an exchange of verse.

ON THE PLANTING OF THE TREES—APRIL 1933

I

May these trees thrive, take root and grow
With arms uplifted high—
So that the Chief may always know
How friendships reach the sky.

2

Rise up ye trees
And grow, symbolic—
Sway in the breeze
With grace botanic.

3

Sun and moon and stars and sky
On their woven branches rest;
Spread your canopy on high
Gift of all God's gifts the best.
BL

An acknowledgment: to
Three good friends.

As trees thrive best in friendly earth
Real friendships grow where hearts are sound.
S. G. knows well what friends are worth;
With handsome trees and friends around
He counts himself a lucky guy—
Looks out, and what is it he sees?
A smiling face, a friendly eye,
Good will, and—overnight—four trees!
Four oaks there are where none there were;
Four beauties shifted by command;
Add these to maple, elm, and fir,
And you'll admit that Nature's grand!

Yes, Nature's grand, but friendship's better—
And on this note I close my letter.
S. S. G.

In the following years, these birthdays were again occasions for verse, not all of which, unfortunately, can now be found.

Dr. Goldwater's sixty-third birthday, in 1936, found him in Washington where we sent the following telegram:

To Doctor Goldwater, commissioner of deeds, architect, sportsman, journalist, poet, grandfather and all-around good fellow: Greetings on the commencement of his sixty-fourth year stop May the troubles of the past remain there and nothing but its pleasures be remembered in the serene and happy life which The Three Musketeers wish for him stop As each candle is added to his birthday cake until the minimum of one hundred and twenty may he count life's pleasures by the score and never forget, in youth or in age, the many friends from near and far who wish him well today.
BLJTJG

Dr. Goldwater replied with a poem in which the italics are his own and refer to certain words which he picked out of the telegram:

To 3 Musketeers:

Your birthday greeting duly reached me;
Generously it impeached me.
Clara laughed when she read "*Doctor*";
Knowing me, that almost knocked her!
From the *Deeds* of a *Commission*
For the time, I claim remission.
I am no certificated
Architect, or consecrated
Classic builder or designer;
Hospitals are something finer.
Sportsmanship is just a wish,
Tracking beast, and bird, and fish.
Journalist I thought I might be—
How I know I'd rather right be.
If indeed I were a *Poet*
Wouldn't I and others know it?
Grandfather I'd like to be;
But will Frank acknowledge me?
To be worthy of "*Good Fellow*"
I must change from hard to mellow.
Yet I'm glad to have your greetings,
And I prize our sometime meetings.
Here's my love to 3 good friends,
Whose faithful kindness never ends.

S. S. G.

In 1937, we sent the following, taking a cue from current cable practices of compressing multiple business names into a single compound name; we adopted the joint pen name of Gotubl by using the first two letters of each name. In this, as indeed in practically all of our poems, Bluestone was the main if not the entire author.

HAPPY BIRTHDAY

G o
O ld friend
L eaving us behind!
D amn it all, tho—
W hy aren't we all
A t sea, in a boat, like you!
T elling the waves where they get off
E very day, for eight blessed days!
R egards old dears and bon voyage to you.

Go Tu Bl

In 1938, I can find no poem by us, but there was the following reply from him:

TO GO-TU-BL

If aureated water were as potable
As aerated water's said to be
I'd send to each and every Go-Tu-Bl
A gilded cask, marked "take internally".

But when each member of a group so notable
Has quenched his thirst with knowledge that makes free
And knows that his own thoughts are fit and quotable
He needs no drink mixed by old S. S. G.

So "Hail!" "Shake!" and "Farewell" to Go-Tu-Bl,
You've grown to be what supers ought to be;
Yet you'll admit you wrote a word unwrotable
When you inscribed Hospitiology.

In 1940, the birthday greeting to him was again an acrostic:

G ift of the blessed gods
O f thee we sing!
L ong may your lamp be bright—
D ay, and throughout the night—
W arm, with its wondrous light—
A royal thing!

T o you we drink a toast
E choed from coast to coast
R ight—in our joyful boast—"To S. S. G.!"
GOTUBL

Then the 1941 birthday brought forth the following:

TO S. S. G.

On His Anniversary Day

Let's drink, boys, to our youthful host,
A man well known to fame—
And greet him with a ringing toast,
To glorify his name.

No other towers quite as high,
A sky-scraper is he!
Not e'en the Muse could pass him by
—His words are poetry. . . .

He design-ates and he creates,
His genius knows no bounds!
He draws the plans—and bears the weights,
While others ride to hounds.

So now we mark the great event,
And we three have our say;
God bless that good old scholar-gent'
This Annivers'ry Day!

His couplet reply was as follows:

'Neath distance, time, and silence lies
True friendship's root, that never dies.
SSG

And on his last birthday, in 1942, came this poetic exchange:

TO S. S. G. ON HIS 69TH

The second month—the day was seven
—It occurred in seventy three;
Our hero made this old earth heaven
—He blest us with his company!

Just think! If this had not been so,
And he had stayed on t'other side,
GOTUBL wouldn't learn to know
The friendship of that learned guide.

This bleak earth would have been more dark
Than we can tell in poetry;
He made it all a pleasant lark
With brilliant luminosity!

The next year we write words in rhyme
He will fulfill three score and ten;
And that will be a blessed time
For many more than us three men!

GOTUBL

TO GO-TU-BL

Can mortal ask for more than friends
Who see in one's poor deeds, great ends,
Who view with charitable eye
One's failings, and though they descry
The faults that make one's claims sound hollow
Unfurl their flags, prepared to follow
As though by doughty champion led?
"Who goes there?" "Friend"; thus all is said.

SSG

Dr. Goldwater's verses were not limited to his own birthday; birthdays of others would also inspire him in this direction. Thus, on the occasion of Mr. George Blumenthal's eightieth birthday celebration, when Dr. Goldwater was unable to be present because of illness, he sent a message of felicitations, a poetic *tour de force*, which was read to the assembled guests:

TO GEORGE BLUMENTHAL

On His Eightieth Birthday

Here's to the best of the best of us
One dear to the hearts in the breast of us
Who springs to our aid at behest of us
Whose judgment is true, and the test of us
Though it's seldom he makes a request of us
His ambition demands of the rest of us
The fulfilment of all that he guessed of us

Let us then give a pledge to the guest of us
To exclude all that's wrong from the chest of us
Say goodbye to the doubt that's the pest of us
And take to our hearts as the guest of us
A perfect Mt. Sinai—the nest of us
Thus our love for G. B. is expressed of us.

On another occasion, in 1936, Dr. Goldwater read an Associated Press news item quoting a speaker who criticized American hospitals and claimed that they "just grew like Topsy, with no planned idea of location and economy". Cited as a horrible example was the use of $35 door knobs in an offending hospital. This prompted the following reply in verse, which Dr. Goldwater sent to a few of his friends, as he put it, "for derisive comment":

Go hospitals, and hide your heads diminished;
Exposed for what you are, your game is finished.
And why not? What have hospitals ever done?
They've served the sick, you say? They have like fun;
They've squandered precious millions shamelessly
While rushing headlong onward, aimlessly.
You cannot show me one that has a plan
Says M. F. (though his Council says it can).
Physicians are like tiny Lilliputians
Crushed in the mouths of giant institutions.
Since only by their talents it can live,
The hospital takes whatever M.D.'s give;
It steals their patients, picks their fruitful brains,
To swell the volume of its ill-got gains.
It boasts of doorknobs made of solid gold,
But how it treats the sick must not be told.
Didst ever see a moron in a stupor?
Behold his perfect counterpart, the "Super",
Who, to win fame, has but to shut the door
And stop the entry of the sick and poor.
To trustees, charity's an empty word,
Of medicine not one has ever heard;
The trustee is a monster—nothing less,
His feelings for the doctor pitiless.
Although he would destroy them (the poor fools)
A hundred thousand staff men are his tools
Go hospitals, and hide your heads diminished,
Exposed for what you are, your game is finished.

Epilogue

How come the A. M. A. has never tumbled
Though all the world's aware that Fishbein fumbled?
Wake up, Messieurs, before it is too late
And gently give garrulity the gate.

At another time, he sent us copies of a poem which appeared in the "World-Telegram". This was signed "Taxpayer", but came from his pen:

"OLD HOSPITAL INFESTED WITH ROACHES, MICE AND ANTS" (News item)

To Dr. S. S. Goldwater
Commissioner
Department of Hospitals
City of New York

November 17, 1938

You can step on a roach and you can crush him
But you can't on an ant—you must rush him
Is a louse in your hair?—you must brush him
Let a mouse have his cheese and you'll hush him.

If a critic is lousy, indict him
Though you feel like it, don't try to bite him
If a hospital's old, write a letter
Persevere till they give you a better.

Go back to the Planning Commission
Explain what it is that you're wishin'
It's not news for they know it already
So be calm, there's no need to be heady.

You want twenty new hospitals—twenty!
Twenty's barely enough, it's not plenty
And all must be antless and mouseless
Each guaranteed cockroach- and louse-less.

Since the cost is but fifty-odd millions
Don't worry in this age of billions
So, out with the roaches and out with the ants
We taxpayers always have ants in our pants!

—Taxpayer

To celebrate the 1939 New Year we were regaled with the following:

DESIGN FOR LIVING

Thumbs down upon the ivory tower,
That symbol of a soul turned sour.

'Twere folly all things to refuse
When one is free to pick and choose.

Nature is cruel but also kind;
A melon rates both meat and rind.

Eggs may be eaten soft or scrambled,
Thoughts may be unrestrained or trammeled.

The world is sad, but likewise gay;
There's always a bad and a better way.

With eyes wide open, shape your plan
And wisely, warily, play the man.

HAPPY NEW YEAR
1939

—SSG

Also in 1939, Dr. Goldwater was the recipient of the City Club's Annual Award "For Outstanding Public Service to the People of New York City". His complete reply was given in rhyme and it was not only another perfect example of his facility in verse but a display of another admirable trait, of giving the credit to the loyal associates and assistants who made his work possible.

When a fellow sets out without thought of reward
To serve Demos, he soon learns to be on his guard
For all who thus serve are compelled to take chances
Of vulgar abuse in a thousand nuances.
So it's rather a shock
To receive, not a knock
But the City Club's gift of a swanky award.

I accept the award not so much for myself
As for five thousand doctors, disdainful of pelf,
Who give to the poor all the knowledge and skill
They command, and unflinchingly work with a will.
Although well do they know
For the rules tell them so
That without any pension
And scarcely a mention
At age sixty-five they'll be placed on the shelf.

And now, my kind friends, just see what you've done
Given not one award, but five thousand and one

There are many more, scores in fact, which must await a later date for collection and publication. But as a last example for this purpose, let me record again the last sentence and verse in Dr. Goldwater's address at the opening of the Exhibit at the Hospital, celebrating its Ninetieth Anniversary in 1942, a few months before his last illness.

In closing, let me address these lines to your distinguished President, to your faithful and energetic Director, and to those members of the Board and Staff with whom it was my privilege to be associated for a time in the development of this great institution:

Full many a year has passed since you and I
Began to think in unison, and talk
Of what a hospital is and what it should be.
Well, thoughts like ours do not die a-borning
But, seized by eager wills, emerge as deeds,
By which new shapes are formed, reshaped again,
Until the world about us is part Nature's,
Part our own.

Although we've not achieved
The perfect institution of our dreams—
Of love, and art, and science all compact—
Rejoice we may, for we have lived to see
The hospital we cherish yield to change
From small to great, from careless to exact,
From home of sorry pestilence to proud
And comely scene of perfect cleanliness
Equipped with all that science knows to aid
Physician, nurse, and sick, to whom in honor
We pledge again our faithful, firm support.