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VITAMIN C: FUNCTIONS AND REQUIREMENTS[1]

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Ascorbic acid is one essential to that "fixity of the internal environment (which) is the condition of the free life" in the words of Claude Bernard. Therefore, understanding of the function of this vital substance is much to be desired. That we know as much as we do about ascorbic acid is due to the intensive research so characteristic of our time. That there should be so much doubt about our knowledge is due to the same thing for the subject is bedevilled by overwriting and incomplete and contradictory reports.

Szent-Gyorgyi isolated ascorbic acid while studying cellular oxidation. The first things he knew about it were that it was in adrenal tissue and reduced silver nitrate. He called it "ignosic" acid because it resembled a sugar he called "ignose." When the editor of the journal to whom he sent his report objected to "ignose" Szent-Gyorgyi proposed the name "God-nose." This was still more objectionable so it was called hexuronic acid, which, as it turned out, was quite incorrect. The discovery of the vitamin was, therefore, somewhat accidental. As Szent-Gyorgyi said, "I became a father without wishing it, the father of a vitamin. Such accidents seem to happen even in science" (1).

Quite naturally the circumstances under which ascorbic acid was discovered and its outstanding oxidation-reduction capacity suggested it might function in tissue oxidation. Its oxidation proceeds through two stages the first of which, the formation of dehydroascorbic acid, is physiologically reversible. Both this and the reduced form are antiscorbutic. The theory that its primary function in the body might be in tissue oxidation was supported by its evident capacity to serve in such a manner and certain other observations. Thus, it is in some ways similar to glutathione, a respiratory catalyst; it reduces cytochrome and increases oxygen consumption in the tissues of scorbutic animals. Indeed, Borsook and associates (2) expressed the opinion that glucose, glucose dehydrogenase plus coenzyme, glutathione, ascorbic acid, a hemochromogen and oxygen constitute a complete respiratory system in which a metabolite is burned and oxygen used. No proof of such an action is available and the work of King and his colleagues makes this explanation seem rather unlikely.

[1] Read April 23, 1940 at the Blumenthal Auditorium of The Mount Sinai Hospital as part of the Symposium on Vitamins.

Little is known about the substances involved in the oxidation and reduction of ascorbic acid. Glutathione appears to be mainly responsible for its reduced state in animal tissues. Various substances capable of forming copper complexes inhibit the oxidation of ascorbic acid presumably by interfering with copper catalysis. Copper seems responsible for the "ascorbic acid oxidases" recovered from plant juices by various workers. Copper plus albumin has the characteristic properties of these enzymes and copper inhibitors, such as potassium ferrocyanide and sodium sulfide, poison the enzymes (3).

The factors responsible for its oxidation are no better understood. Increased oxygen consumption by scorbutic tissues following the addition of vitamin C is not considerable and no more than the vitamin itself would account for. It seems, therefore, that ascorbic acid is not a major respiratory agent. This does not mean it is not important in the metabolism of animals but not in the manner postulated.

We do know it is synthesized by all the higher plants, probably by simple organisms such as yeast and bacteria and by all studied animals excepting the guinea pig, man and other primates. It has been suggested that vitamin C is formed from sugars, to which it is so closely related. In sprouting seeds the addition of various sugars increases the amount of vitamin C formed but no one sugar is particularly active. Guha and Ghosh (4) claimed that rat liver, spleen and other tissues formed vitamin C from mannose both in vitro and in vivo and similar results were reported from clinical experiments, but their work could not be confirmed. Inanition causes a rapid and pronounced loss in vitamin C excretion in the rat but no article of diet has been found which selectively corrects this defect. The substances which increase vitamin C excretion are unrelated and probably function as stimulants of its excretion or its formation from intermediate metabolites.

Thus far, therefore, the chemists have not reached very definite conclusions. Let us consider scurvy itself to see if it affords some clue of the action of ascorbic acid.

There are two views of the pathogenesis of scurvy. Both are interpretations of the lesions in the skeletal system. One theory is that ascorbic acid is essential to the structure and function of the fibroblasts and osteoblasts and through them affects their products, collagen and bone. The other theory is that the ascorbic acid is an ingredient of collagen, causing collagen fibers to form by gellation in the intercellular fluids. The gellation theory was first suggested by Aschoff and Koch (5) in 1919 and has found its greatest support in the studies of Wolbach (6). The most important observations are of the state of absolute scorbutus and the immediate response to ascorbic acid. They consist essentially of the observation that two major phenomena occur in complete deprivation. Intercellular substances . . . collagen has been most carefully studied . . .

fail to form. In the intercellular spaces is seen only a fluid material which stains poorly or not at all. A second phenomenon is that blood clots and wounds, in scurvy, are avascularly organized. Capillary endothelium is present in clumps and nests and the cells multiply but appear unable to form capillaries. Administration of ascorbic acid causes rapid formation in the intercellular fluids of broad bands of collagen, and by the endothelial cells of capillaries.

Wolbach's view originally seems to have been that the cells played a minor role in the formation of the collagen since it was deposited at some distance from them. In a later study, however, he states that collagen is secreted by the cells, that its arrangement is determined by their arrangement and the arrangement of their processes including fibroglia fibrils.

Whichever view is correct there is no reason to doubt that deterioration of existing intercellular materials and their absorption are the prime anatomical characteristics of scurvy and that all of the lesions may be so interpreted. Observations of bygone days may be so explained. The softening of bone callus, the opening of old sabre wounds, periosteal hemorrhages and separation, the weakening of arteries are patently due to this deterioration. In the guinea pig, for example, the head may be inadvertently torn from the body during skinning because the ligaments are so weakened.

It seems to me that these phenomena are our best clue to the action of ascorbic acid and I regret that they have not been as thoroughly studied as those I first mentioned. I should like to take some minutes in describing what is known of collagen formation.

The studies of Heringa and Lohr (7) indicate that collagen formation is of the nature of coagulation in a colloid solution with rod-shaped micellae. Nageotte (8) suggested, on the basis of tissue culture studies that the collagen fiber was a non-living structure produced by coagulant ferments and that its repair was similar to that of a broken crystal. He later succeeded in recoagulating dissolved collagen with salts of univalent metals. I may say that judging from his photographs he succeeded in artificially forming what must have looked like collagen. He doubted that it was secreted by fibroblasts and thought it came from elsewhere in a dissolved state and was only coagulated through the influence of various kinds of cells. It would be interesting to apply the Hoffmeister series to this experiment.

Some years later appeared a communication by Wolf (9), who observed the formation of collagen fibrils in cell free cavities within certain cartilages of cattle and men. He considered the process completely acellular and reported he was able to obtain true collagen fibers in the absence of cells, in vitro, from fluid taken from such cavities. The same year Clark (10) described Laue diagrams of collagen, bones and teeth. She was able to verify earlier reports of the diagrams produced by collagen, indicative of

an amorphous or liquid crystal condition. Drying and stretching both resulted in typical crystal patterns. Bone yielded similar patterns plus apatite or calcium phosphate crystals. Her conclusion was that collagen exists in an amorphous form but that the micellae may become crystalline.

This work seems to offer very strong evidence of the structural character of collagen and also an explanation of a related phenomenon of scurvy. For during scurvy bones do not calcify; osteoporosis occurs. According to present theories of calcification two mechanisms may be postulated to explain the calcification of bone; the phosphatase mechanism by which an enzyme present in ossifying bone hydrolyzes phosphoric ester thereby increasing the inorganic phosphorous and producing supersaturation and the second, or inorganic mechanism, by which calcium phosphate is deposited from super-saturated solutions. Since cartilage collagen in a colloidal form has great absorptive powers for calcium and will accumulate it to the point of saturation a change in the character of the sol, crystallization, would induce precipitation. Is it not reasonable to consider that the first mechanism, that of phosphatase, is involved in rickets, since we know that changes in phosphatase do occur during that disease, and that the second type of reaction is involved in scorbutus in which sudden physical changes are known to occur in the ground substance of bones?

In further substantiation of the nature of the formation of collagen may be mentioned the tissue culture studies of Maximow (11), who stated the fibers are the product of the crystallization of certain substances in the medium and that various cells besides the fibroblast serve to induce their formation. The early studies of Baitsell (12) and the later ones of McKinney (13) suggest similar conclusions. Still later von Jeney and Törö (14) succeeded in controlling the formation of fibrils in tissue cultures by the addition of ascorbic acid.

The correct explanation of these changes is unknown. It is very well known, however, that hydrogen ion concentration is of critical importance to colloidal systems such as the collagen precursor appears to be and it may therefore be perfectly true that Szent-Gyorgyi's original suggestion of the action of the vitamin is in general correct, but that the effect is apparent only in the specialized tissues of the skeletal system, or is primarily active there.

I mentioned that the effect on collagen was responsible for various dramatic lesions observed by our predecessors. It is responsible also for some of the soundest observations of the possible importance of ascorbic acid today. Thus wounds will not heal during severe depletion. Von Jeney and Törö (14) reported animals in which wounds failed to heal in from 17 to 23 days. Chronic scurvy, i.e. partial depletion, retards healing. Cellular union occurs but either no scar or an inferior one. More recently various reports on this have appeared, all in agreement. The tensile strength of wounds has been determined, the levels of ascorbic acid intake

necessary to proper union and other things. I may say that interference with healing has not been reported except in rather severe degrees of depletion. Some authors have described poor union in subclinical scurvy, but I do not feel their data justifies this interpretation. I do believe that in certain cases of peptic ulcer, patients in whom in my own experience as well as that of others, depletion of ascorbic acid is surprisingly common and severe, this may have clinical importance. At any rate it is interesting that such patients are notoriously disposed to poor post-operative union.

Beyond the healing of wounds lies the formation of granulomatous lesions. During scurvy very little fibrosis, and that very delicate, appears. Treatment causes the prompt appearance of heavy sheaths of collagen. Aschoff and Koch (5) recognized this in human material; it was experimentally studied by Höjer (15) in his fine work on guinea pig scurvy. It has repeatedly been verified since. It has probably been responsible for the sudden spread of tuberculous infection in certain circumstances but I doubt very much, because of what we know of the levels of depletion needed for its occurrence, that it occurs but rarely today in our own country. It is true that the average case of tuberculosis has subnormal levels of blood ascorbic acid but hardly of a degree which might cause defective callus.

The speed with which morphological changes occur in intercellular substances is only exceeded by the changes in the capillaries although allowing for the differences in the criteria used in estimating these effects they are of the same order. Indeed it was the promptness of response in the lesions in the ribs which led me, in 1930, to attempt to measure the capillary effect (16). Capillary fragility, in the guinea pig, largely disappears within a few hours of the injection of vitamin C or, as I used it, the injection of sterile, neutralized orange juice.

The minute structure of the capillary wall is not well known. A cement substance has been postulated. Is it not more likely, in view of what we know of semi-permeable membranes that this is also colloidal? Under these circumstances it might well respond as the collagen does to ascorbic acid.

There is no evidence of disturbed capillary function. Some years ago Rous and Smith (17) observed the diffusion rate of various dyes through the terminal vessels. Dr. Rous tested a number of my scorbutic guinea pigs and found no deviation from normal.

I was surprised in following the effect of depletion on the capillary resistance of guinea pigs to find that the resistance did not constantly decrease but was subject to a transient rise to nearly normal values during the second week of the disease. This adaptation, if I may call it that, has received very little attention although it has since been noted. Thus, Giroud (18) found that severely depleted guinea pigs first lose tissue vitamin C and then the values rise. Under the levels of feeding of his experiments a low was reached after 15 days and a temporary high after 30 days.

Wachholder (19) also found an immediate severe loss of tissue vitamin followed by a transient increase. Wachholder found similar fluctuations in human cases. Likewise Baucke (20) found that while the metabolic rate of guinea pigs on a basal diet diminished to 50 per cent of normal, transient rises occurred just before symptoms appeared and again before death. Aschoff (21) stated that during the first World War troops on leave were more susceptible to deficiency than the home folk who seemed to have adjusted to their poor fare. Observations of this kind are no more than clues although, it seems to me, very interesting ones for they imply an ability to compensate for dietary deficiency.

It is generally believed that animals other than the guinea pig, man and other primates are immune to scurvy because they are capable of synthesizing vitamin C. Is it possible that this difference is only relative? It would be more harmonious with other biological knowledge if it were. This is a particularly significant problem because it touches on the etiology of scurvy and on our requirements of ascorbic acid.

I think the best introduction to this subject will be a brief review of "rat scurvy." Twenty years ago, when the experimental study of scurvy was beginning the behavior of the rat on scorbutogenic diets occasioned much concern. Of course our knowledge of the vitamins was very limited at the time. Milk was considered a complete food. The demonstration by Jackson and Moore (22) that milk and oats did not protect guinea pigs against scurvy was cause enough at that time to discredit the theory that scurvy was a deficiency disease. The following year McCollum and Pitz (23) said scurvy was a symptom of constipation, that lemon juice acted simply as a cathartic. These theories were indirectly supported by the general observation that on the same diet rats thrived and guinea pigs died. The experiments of Parsons (24) supplied an explanation. Parsons showed, by feeding the livers of depleted rats to guinea pigs that the rat maintained a tissue supply of vitamin C wholly independent of its dietary intake. But the following year the subject was thrown into confusion again by the announcement by Shipley, McCollum and Simmonds (25) that they had succeeded in producing scurvy in rats by dietary means. Unfortunately the diagnosis was not very satisfactorily established. I remember feeding a diet completely deficient in vitamin C to two generations of rats and searching them carefully for lesions. I found none.

Some years later, however, Kollath (26) said he was able to produce scurvy in rats by feeding them a vitamin B deficient diet in which cottonseed oil was replaced with peanut oil. Using cottonseed oil vitamin B deficiency developed, on peanut oil scurvy. Schmorl was said to have verified the diagnosis by histologic examination but his findings were never reported. As far as I know Kollath's experiments were never repeated elsewhere. But I believe they have now been explained for Muselin,

Tully, Longnecker and King (27) have discovered that certain lipids cause ascorbic acid depletion in the rat. The vacuum-distillable fractions from the unsaponifiable matter of halibut liver oil, oat oil, grass leaf oil and alfalfa leaf oil were active, as well as various cyclic ketones. The common fatty acids, sterols, proteins and sugars were not. There has still been no description of the lesions of scurvy in the rat but the other evidence is very satisfactory and Vedder and Rosenberg (28), who were able to repeat their work report that the symptoms can be very largely controlled by ascorbic acid which seems to be definite enough. With some reservation we must be prepared to admit that rats are not rigidly immune to scurvy. To complete a review of "rat scurvy," I should add that there were clues to this development back as far as 1918. In that year Harden and Zilva (29) described experiments in which rats on a classical scorbutogenic diet "did not thrive so well as animals which have their diets supplemented with an antiscorbutic." Such animals did, however, continue to grow and gain weight and remained free of symptoms. Since at that time a supplement of antiscorbutic meant fresh vegetable or fruit such experiments were subjected to the criticism that more than vitamin C was given the control animals. But in view of subsequent reports and the evidence on the forced depletion of rats I think we may assume that the rat is not independent of ascorbic acid.

Other bits of information are pertinent. The deer is said to be susceptible (30). Hjarre and Lilleengen (31) found classical scurvy lesions in calves and say that the disease quite commonly occurs spontaneously during late winter in Denmark, Germany and France. Zilva and his colleagues (32) claim the observation of scurvy in swine.

Thus, the difference between species appears to be only one of degree. Since the immune animals are known to synthesize ascorbic acid it seems reasonable to assume that man may do this likewise although not very effectively. So far as I know this has never been taken into consideration in discussing the human requirements of vitamin C although its practical importance has been suggested in pregnancy. Various students have believed that the fetus is capable of synthesizing ascorbic acid and this has been offered as an explanation of the relative immunity of the pregnant woman to scurvy. In this case, too, the immunity is only relative and congenital scurvy is well known although quite rare.

The question is just how independent is man of an external supply of ascorbic acid. Is synthesis increased by depletion, by the nature of the other nutrients? Are other conditions besides depletion necessary for the production of scurvy? This problem was very bluntly stated last year by Rietschel and Mensching (33). Mensching remained on a vitamin C free diet for 100 days, interrupting the experiment only for the Christmas holidays. Throughout that time he felt perfectly well and was free of signs of scurvy. His gums remained normal, his teeth did not fall out.

He did not develop capillary fragility. He gained in weight. Yet his blood plasma ascorbic acid at the end of the experiment had reached an imperceptible level. There are other instances of such periods of depletion in which the diet was in other respects ample and in which scurvy did not appear. Rietschel and Mensching suggested three explanations, synthesis, re-use or the existence of other antiscorbutic substances.

This gross discrepancy between observations in the laboratory and the field moved Stefansson (34), the explorer, to write last year that Eskimos should all have scurvy if our estimates of their requirements are correct and their food actually contains as little vitamin C as our tables show. Actually they do not have scurvy. Of course it is easy to haggle over both these discrepancies. Eskimos may obtain ascorbic acid in special ways, as the North American Indian ate the adrenal glands of moose. Mensching may actually have secured more vitamin C than he believed, in the case of some dishes he relied on overcooking to destroy the vitamin. But this would hardly explain the absence of vitamin from his blood plasma at the end of the experiment.

Another fact which requires careful consideration is that our large epidemics of scurvy have occurred during periods of general privation. Armies have starved, and become scorbutic. The ration served in the Royal Navy in the 18th century (35) could not by any stretch of the imagination be considered an adequate, well balanced basal diet.

Physicians have suspected that the etiology of scurvy is somewhat complicated. In 1917 Hess (36) wrote: "Infantile scurvy is not, however, a simple dietary disease. The diet is at fault in allowing the intestinal bacteria to elaborate toxins." Brennemann (37) said: "Scurvy occurs only in children with a predisposition to the disease . . . and the individual factor may play a larger part than we now know." Such views were based on clinical observation of the discrepancies between diet and the occurrence of scurvy. On the same intake not all individuals develop the disease. Scurvy sometimes fails to recur although the diet is not changed. On the same diet one group of individuals may develop scurvy, another neuritis.

These clinical theories have been in eclipse because by present standards they were not supported by adequate evidence. But they may be quite correct. It would not be the first time that nutritionists rediscovered something known years ago by physicians. At any rate, whatever the explanation, if a man can exist on a diet completely or almost completely devoid of ascorbic acid for 100 days and remain well are we justified in urging people to take 50 mgs. a day?

A very popular conception during recent years has been that partial degrees of depletion, mild or subclinical scurvy, is very common, that many Americans secure less than an optimal intake of vitamin C. Is this correct?

The conception of subclinical scurvy arose from guinea pig studies. Twelve years ago vitamin C was measured by feeding experiments and a

tremendous amount of animal assay work was being done. Vitamin C potency was determined by the amount of unknown substance necessary to protect a guinea pig against scurvy. The weight curve plus certain gross observations furnished a method of grading the disease. But it was soon found that an animal might look well and grow properly and still have lesions of scurvy, in particular in the teeth which are very sensitive to deficiency. This zone between clinical scurvy and complete protection as determined by histological inspection was identified as subclinical scurvy. The supposition was that a similar condition occurs in man.

The earliest evidence that it did was based on capillary resistance tests (38). By discounting all of the other factors besides vitamin C deficiency which might cause capillary fragility it was found that a great many individuals not only had capillary fragility but that improvement in diet corrected the condition in most cases. There has been much criticism of the capillary resistance test, but the basic observation has been confirmed by many careful workers and I think it is quite reliable. At any rate, once the chemical methods were popularized it was found that they too showed that low excretion, low blood plasma levels and unsaturation were common. Both the capillary tests and the chemical tests indicate that, roughly speaking, about one-fourth of the general population is partly depleted of vitamin C.

It would doubtless be a long step forward if we could measure the slightest degree of deficiency. Then we could at least establish minimal requirements for health. In certain respects the capillary test seems more significant than the chemical methods since it does reveal morbid function or structure. This the chemical tests fail to do since their values are arbitrary and, in individual cases at least, depletion may be present without symptoms. But the capillary test is not specific enough to be thoroughly satisfactory and must be improved or replaced.

What other criteria do we know about which might serve? Complement diminishes in depletion, both in the guinea pig and man as Ecker's studies (39) so plainly show. The inferior nature of winter complement is due to subclinical scurvy. But complement is influenced by other factors than vitamin C. Resistance to infection is diminished by partial depletion. An experience of my own illustrates this very well. At the old New York Hospital guinea pigs inoculated with material suspected to contain tubercle bacilli were given a large dose of old tuberculin some weeks later. If they had been infected they usually died shortly after the tuberculin was given. When I went to Grasslands Hospital I introduced this method. It was one of the first suggestions I made in my new post and I was very disturbed when it failed to work. It was several years before an explanation occurred to me. Grasslands Hospital is located in the country and the animals are fed a model diet. In the old New York Hospital they were poorly housed and indifferently fed. Since then many studies have

demonstrated the relationship between vitamin C nutrition and sensitivity to tuberculin. Extensive tests have been made by Steinbach and Klein (40). In their most recent experiments the mortality rate among infected guinea pigs given large doses of tuberculin was decreased to less than one-fourth by administering 5 mg. of ascorbic acid daily. But resistance to infection offers nothing useful as a clue to the measurement of the adequacy of a diet because it is influenced by innumerable forces.

Even were we able to determine the minimal intake necessary for complete protection we would be far from knowing the optimal requirement. Optimal nutrition is very difficult to identify and measure, particularly, of course, in man. What, for example, shall we take for our normal controls? We have no adequate standards. As Lydia Roberts (41) put it, we are like a man setting out to raise peaches who has never seen a ripened peach, and has no knowledge of fruit cultivation. But he plants his trees and in spite of poor soil and ravishing insects manages to get a crop of undersized, green and gnarly peaches, which he and his friends consider to be very fine. But one day a friend who has been raised in the peach country comes along and ridicules the crop. "Do you call those miserable things peaches?", he asks. The novice cannot understand his friend and says, "They are all right no matter what he says. Anyhow, he is a fanatic and must have been looking for watermelons instead of peaches."

Giroud (42) has made an interesting suggestion. Since the end point of scurvy is difficult to recognize, why not, he asks, consider the concentration of ascorbic acid in certain organs of species immune to the disease to represent physiological norms? Thus, the rat adrenal contains 1.75 mgs., the liver 0.25 mgs. per gm. Presumably in this animal, independent of dietary supply, this value has some significance, perhaps to the adrenal itself. These values are from two to three times as great as Yavorsky, Almadan and King (43) found in human tissues. The distribution of ascorbic acid throughout the animal does suggest a functional relationship. In order of concentration the organs may be listed as follows: adrenal cortex, brain, pancreas, liver, spleen, kidney, lung, heart and thymus. Glick and Biskind (44) extended these observations by assaying the ascorbic acid in various parts of particular organs. They found, for example, that the pars intermedia of the pituitary was even richer in vitamin C than the adrenal cortex, that corpus luteum contains much or little depending on its own activity. The distribution of vitamin C within the cell itself suggests a functional importance (45).

If we adopt some such standards, or rely on the chemical tests we may, perhaps, be able to make reasonable estimates of the average requirement. But the requirement of any given individual, and particularly a sick individual, will be modified by other circumstances. Many of these are obvious, fever, increased metabolic rate, diarrhea, nephritis and other disturbances which modify requirements or absorption. But there are much

more interesting forces involved. We might say that, like peace, nutrition is indivisible. I will mention two examples of this. One of Kollath's latest papers (46) describes the behavior of rats fed a basal diet of casein, rice starch, peanut oil and potassium phosphate. On this basal diet the duration of life is only four weeks. Supplemented with thiamin and cod liver oil the diet supports life for an average of two years. Growth is retarded, cataract, icterus, emphysema and chronic nephritis are common. But no signs of known deficiency disease appear although the diet is quite frankly lacking in several vitamins, including ascorbic acid, as well as minerals. The effect is not a number of deficiency diseases but a condition sui generis. I venture to suggest that under these circumstances the requirement of various vitamins is quite different from what it would be if the basal diet were complete except in a single nutrient.

The second example is also a recent observation. Spies writes (47) that when pellagrins living at home are given supplements of nicotinic acid, thiamin and riboflavin they frequently return to the clinic with eye signs of vitamin A deficiency. These signs, it should be noted, do not appear until the other deficiencies are corrected. There are, of course, many instances of multiple deficiency disease but to a considerable degree the requirement for each particular vitamin is determined in part by the presence of other vitamins and nutrients. Probably the classical example of this effect is the requirement of thiamin in terms of caloric intake. The Japanese develop beriberi not only because their vitamin B_1 intake is low but also because their diet is very high in carbohydrate.

Neither can we disregard the irreversibility of certain deficiency effects. It is not alone what we now eat that determines our physical constitution but what we formerly ate. In the study of Kollath and Giesecke just referred to this was clearly apparent. After rats had subsisted on the experimental diet for some time it was impossible to repair the damage done. Only a complete diet from earliest youth assured health. This is also true of the other deficiency diseases.

The eating habits of generations have given us certain prejudices. When Zilva objected to feeding guinea pigs four times as much ascorbic acid as was needed to prevent scurvy Szent-Gyorgyi replied that such animals living in their natural habitat actually do consume ten times the amount needed to prevent scurvy. Various men have measured the vitamin stores of wild animals and found enormous concentrations. Primitive peoples similarly appear to supply themselves more generously than we do. We might say, in criticism of much of the nutritional research of the past twenty years that it has aimed at finding diets which cause disease rather than diets which insure good health.

The story of vitamin C, if I read it correctly, is not a closed book. It is a book in which we have only turned the first pages.

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ABDOMINO-ENDOANAL RESECTION OF THE RECTUM AND RECTOSIGMOID FOR LYMPHOGRANULOMA VENEREUM

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Lymphogranuloma venereum has recently increased materially with the influx of a Porto Rican population and, while it is mainly confined to the negro race, it may occur in whites. The etologic agent is probably a filterable virus. According to Kornblith (1), the secondary adenopathy in the female affects chiefly the intrapelvic glands, and the subsequent inflammatory and cicatricial reaction in the endopelvic fascia leads to the genito-ano-rectal syndrome. The pathologic picture is that of a chronic, non-specific inflammation, suggestive somewhat of syphilis, but the presence of a negative Wassermann, the absence of tuberculosis, and a positive Frei reaction establish the diagnosis of lymphogranuloma venereum by exclusion. As a rule, the glands show a characteristic lesion of focal necrosis, perivascular plasma cell infiltrations, endophlebitis and a focal accumulation of epithelioid and giant cells of the Langerhans type.

In the following case, the etiology of the stricture of the rectum was not recognized until three years after the onset of symptoms when a Frei test was performed and found to be positive. Inasmuch as the lesions were progressive and had failed to respond to conservative therapy, surgery was resorted to.

CASE REPORT

History (Adm. 407246). This married female, age 30, was first admitted to the Surgical Service on October 26, 1930 and discharged November 3, 1930. At that time she gave a history that for the past eight months she had experienced the frequent passage of a thick mucoid substance from her rectum, unaccompanied by feces or blood. During this period there was anorexia and a loss of about fifty pounds in weight.

Examination. About an inch above the anal margin, a stricture could be felt which admitted a finger. Encircling the entire rectum at this point was a fairly firm, irregular mass, the upper limit of which could be outlined by the examining finger. It did not feel like a neoplasm.

Laboratory Data. The rectal smear was negative for ova and parasites. The vaginal smear was negative for gonococci. The Wassermann reaction was negative. Stools were only faintly guaiac positive. Proctoscopy showed the mucosa to be thickened, reddened, and irregularly granular but without ulcerations. The stenosis was situated about 4 cm. above the anus. The biopsy was reported "granulation tissue showing chronic and acute inflammation." No glandular structure was seen.

Course. The lesion was considered to be inflammatory and the patient was referred to the Out-Patient Department for rectal dilatation. In spite of treatment, she still complained of a mucous discharge.

Interval History. On February 27, 1933, a Frei test was positive with both antigens. Lymphogranuloma venereum involving the rectum was now diagnosed. The constipation gradually increased and there were intervals in which no bowel movement occurred for ten to twelve days. Cathartics induced frequent small movements accompanied by tenesmus. There was a persistent yellowish and serosanguinous discharge which at times was faintly bloody.

Second Admission. Inasmuch as conservative therapy gave no relief, she was readmitted to the surgical service on April 16, 1937 and discharged May 11, 1937. The rectal examination at this time revealed a stricture extending upward from the anal margin and formed by irregular granulomatous masses with several polypoid-appearing excrescences. A barium enema revealed the presence of a rectal stricture extending into the rectosigmoid. The patient was prepared in the usual manner and on April 24, 1937 exploration was performed through a lower left rectus muscle-splitting incision under spinal anesthesia. The distal fourth of the sigmoid was edematous, thickened, and covered with patches of fibrin on its anterior surface. In the region of the rectosigmoid and extending toward the rectum, a definite brawny induration could be felt. The uterus, tubes and ovaries were normal. A typical abdomino-endo-anal resection of the rectum and rectosigmoid was then performed. A point was chosen opposite the promontory of the sacrum and the superior hemorrhoidal artery was ligated. The vessels of the mesentery of the sigmoid were divided in such a way as to preserve an adequate blood supply to the sigmoid which was to be subsequently implanted through the rectal sphincter. The rectosigmoid and rectum were then dissected from the hollow of the sacrum. A U-shaped incision was made in the pelvic diaphragm so as to dissect the rectosigmoid and rectum from the lateral pelvic walls and from the upper part of the vaginal wall. The middle hemorrhoidal vessels were ligated. After the bowel had been adequately freed, the redundant rectosigmoid and lower part of the sigmoid were tucked into the hollow of the sacrum and the pelvic peritoneum was closed about the sigmoid at a new level. The abdominal wall was closed in layers using chromic sutures throughout with pincettes for the skin. The patient was then placed in the lithotomy position and an endo-anal dissection of the rectum from the sphincters was accomplished and the anal portion of the rectal canal was closed with a purse-string silk suture. The sphincters of the rectum were then dilated. The dissection of the rectum was then continued and it was freed from the lower vagina and the levator ani muscles. The rectum and rectosigmoid could now easily be drawn through the sphincter. At about one-half inch under proximal to the diseased sigmoid a ligature was placed about the sigmoid and the bowel was divided. During the course of the dissection, an opening was made through the posterior vaginal wall which was closed. A new diaphragm was restored by the suture of the levator ani muscles about the sigmoid. Four small pieces of iodoform packing were placed at 12, 3, 6 and 9 o'clock about the sigmoid up to the levator muscles.

The Pathologist's Report: "Specimen consists of 19 cm. of the rectum, anal canal and perianal skin. The upper 11 cm. of the anterior and lateral wall are covered by a shining peritoneal surface dotted by a few hemorrhagic areas. The perianal fat is somewhat thickened. The specimen has already been opened. Approxi-

mately 1 cm. of normal mucosa is present at the upper end terminating in a serpiginous border. From this point to the perianal skin, the mucosa is abnormal. It is almost entirely ulcerated leaving small irregular and thin islands of mucosa separated by varying sized areas of exposed submucosa and even muscularis. On the anterior wall just above the ano-cutaneous margin is a deeper ulceration 2 cm. in diameter. The margin is almost punched out while the base is covered by a through layer of granulation tissue. The muscularis appears thin in places while in other areas it is edematous. The perianal skin shows no gross abnormality.

Diagnosis: Chronic ulcerative proctitis with foreign body reaction but otherwise non-specific. Small lymph nodes attached with sporadic small foreign body tubercles. No histologic evidence of lymphogranuloma."

Patient was immediately transfused after operation. The projecting sigmoid was viable and it was opened after twenty-four hours. The bowels moved four days after operation. The packing was gradually removed and the sigmoid soon became adherent to the sphincter and skin. A Frei test, repeated on May 7, 1937, was reported positive.

The patient was discharged seventeen days after operation. She was last seen October 19, 1938, at which time she weighed 195½ pounds having gained fifty pounds. She was able to control the bowel movements. On examination, there was a prolapse of mucous membrane for a distance of about an inch, and fibrous stricture was found below the mucous membrane, which felt perfectly normal. There was some muscular action, as determined by the ability of the patient to tighten the lowermost part of the anus around the examining finger. Whether this was the levator or sphincter ani muscle was difficult to say.

COMMENT

The only apparent method by which cure may be effected in cases of lymphogranuloma venereum, in which the rectal physical findings indicate progression in extent, is by radical excision of the lesion. While the disease invariably starts in the rectum, it may spread to the sigmoid, as in this case, and it has been known to involve the entire colon. In the majority of cases, provided that the physical condition of the patient will permit, a loop colostomy with a subsequent perineal excision of perianal skin, the anus, the rectum and rectosigmoid, is probably the operation of choice. A very satisfactory series in which this procedure was employed has recently been published by Edwards and Kendell (2). It was felt, however, that the case herein described would lend itself to an abdomino-endo-anal excision of the rectum and rectosigmoid with preservation of the sphincters. This procedure, advocated originally by Villard and Ricard (3) in carcinoma of the rectum, has been extended to include selected cases of rectal lymphogranuloma venereum.

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INFLUENZAL MENINGITIS

Recovery in a Girl Aged Eight Years

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The prognosis of a number of infectious diseases has been completely altered in the past few years, due to the introduction of entirely new methods of treatment. One of the most striking instances is that of meningitis due to the influenza bacillus. Bloom (1) collected from the literature up to March 1930 a total of 302 cases with a mortality of 92.05 per cent. Neal, Jackson and Applebaum (2) in 1934 reported 111 cases of this disease with 4 recoveries, a mortality of 96.4 per cent. Silverthorne (3) and his associates reported 70 cases treated before 1930 with a mortality of 98 per cent. In contrast to these figures, one may now find in the literature numerous reports of recovered cases. I wish to report here a severe type of meningitis due to H. influenzae in a girl aged 8 years ending in recovery. Incidentally, it is of interest to note that during the past ten years, 17 proved cases of influenzal meningitis were treated on the medical wards at The Mount Sinai Hospital and that this is the first one to end in recovery.

The improvement in the prognosis of influenzal meningitis apparently depends on the introduction of specific serum and the chemical drugs of the sulfanilamide group. Specific serum was first used in 1911 by the late Martha Wollstein, who immunized goats with strains of H. influenzae. Immune horse serum was used in the four recovered cases reported by Neal et al., but as the authors themselves state, it was not given early in the disease or in large enough amounts to appear to have influenced the outcome. In their conclusions, they make the following statement: "At present there is no adequate method of treatment. Further research should be done toward the development of a more potent serum with high antitoxic as well as antibacterial properties." During the past six years much work has been done along these lines. In New York City, the Health Department now puts out a serum made by immunizing horses. In Boston, a potent horse serum has been prepared by Fothergill and has been used in a large series of cases (4). This investigator advises that with the injection of the antiserum, complement (either human or guinea pig) be injected at the same time. He has shown that "in only occasional cases of meningitis is complement demonstrable in the cerebrospinal fluid." As the immunological mechanism in destruction of the bacteria by the antiserum is a complemental bacteriolysis, he believes complement should be added when administering the serum. Not all authors are in agree-

ment with this. Fothergill reports on 201 cases treated by his method with 31 recoveries, a mortality of 84.6 per cent. Among these 201 cases is a group of 36 reported by Silverthorne (5) in which 10 cases recovered; a mortality rate of 72 per cent. These authors comment on the use of a continuous intravenous drip of 2 parts of 5 per cent glucose and 1 part of normal saline solution. They believe that this procedure may promote an increased flow of cerebrospinal fluid when a lumbar puncture is done and thus improve spinal drainage.

In February 1939, H. E. Alexander (6) of the Babies Hospital in New York City published a brief report of work done with rabbit serum. This work is based on a certain parallelism between the reactions of the H. influenzae and the B. pneumococcus, as shown by Pittman. Alexander points out that all the strains of H. influenzae found in cases of meningitis belong to one group, type B. As this type has a capsule, typing is performed by the capsular swelling method, as is done with pneumococci. Basing her reasoning on the work of Goodner and Horsfall, she uses rabbits to produce her antiserum, believing that the smaller size of the anti-carbohydrate molecule of the rabbit serum allows it to penetrate tissues more easily, thus crossing the "blood-cerebrospinal fluid" barrier with less difficulty. She uses the whole serum intrathecally but uses a globulin fraction intravenously.

Sulfanilamide and its derivatives have been used for various types of meningitis, including the influenzal, since Long and Bliss showed that sulfanilamide was effective in inhibiting H. influenzae *in vitro* in a concentration of 1:10,000. There are a number of cases of influenzal meningitis which have been reported cured with the use of these drugs alone (7).

In September 1939, Hamilton and Neff (8) reported the cure of a two year old child. Treatment was begun on the second day and consisted in the oral administration of "Dagenan" (sulfapyridine) for 25 days. The dose varied up to 1.5 Gm. per day. The blood culture was positive, as were the first three cerebrospinal fluid cultures. Fever lasted for 18 days. Lumbar punctures were done for 7 days. Recovery was complete, without sequelae.

Following the work of Povitsky, and Branham, and of Rosenthal who showed that mice resisted infection better when treated with immune serum and sulfanilamide than when treated with either of these agents alone, the New York City Health Department advocated combined treatment (9). Many cures have been reported by this method (10). At the present time, the percentage of the recoveries at the New York City Health Department is about 50 per cent (11). In the following case report, this combination of drug and serum was used.

CASE REPORT

Peggy G., aged 8 years, was a first child, born at term by normal delivery. Birth weight was 7 lbs. 4 oz. She had several attacks of cyanosis and difficult breathing

while still in the hospital. A roentgenogram revealed an enlarged thymus, for which she received 3 X-ray treatments. No further dyspnoea or cyanosis occurred. She had a mild club foot which was corrected by exercise and massage. Her first tooth appeared at one year. She spoke words at eight months but made sentences only at two and one half years. She has always spoken with a slight lisp. She sat up at six months and walked at fifteen months. She had varicella in 1936; measles and pertussis in 1938; a tonsillectomy in 1939.

On December 14, 1939 she left her home in Syracuse, N. Y. to come to New York City to consult an oculist concerning the advisability of operation on a congenital squint. Two weeks before leaving Syracuse, she had a mild upper respiratory infection followed by a cough and a foul nasal odor. Two days before her departure, she ate 24 cough drops and drank a whole bottle of cough mixture at one time. The next day she vomited and appeared "groggy" but this was attributed to the cough mixture and she was put on the train at noon. At six P.M. she arrived in New York, very sick, delirious, with a temperature of 104.4 degrees. She was seen by Dr. Fritz Weil, who found the patient markedly prostrated and somewhat irrational. She had a right otitis media, the drum being reddened, but not bulging. There was a marked fetor from her nose and mouth. The pharynx was markedly injected. There was no eruption. The neck seemed somewhat rigid.

The following day she seemed definitely worse. Besides the neck rigidity she now showed a bilateral Kernig and a Babinski sign. A lumbar puncture was done and turbid fluid was obtained. At eight-thirty P.M. she was seen by Dr. Weil and the author. The patient appeared extremely ill. She was delirious, irrational and quite disoriented. She had refused to open her mouth all day and had taken no fluids at all. She was markedly dehydrated, her eyes sunken and her cheeks flushed. All the classical signs of meningitis were present. While examining her, one was struck by the foul odor from the nose. There was not much nasal secretion. By prying open the mouth, the throat could be seen with difficulty. It was deeply congested but no exudate was present. The right ear drum was reddened in the region of Shrapnell's membrane; there was no bulging. The left drum was normal. The eyes showed equal pupils which reacted to light. There was moderate conjunctivitis. There was an internal strabismus. The fundi were negative. There were a few palpable cervical lymph nodes. The heart was rapid but otherwise negative; the lungs showed no abnormalities. The abdomen was soft and not distended. The liver and spleen were not felt. The urine was normal except for a trace of albumen. It was decided to hospitalize her and she was admitted to The Mt. Sinai Hospital that same night.

At the hospital another lumbar puncture yielded a cloudy cerebrospinal fluid under increased pressure; 20 cc. were removed and 420 cells of which 90 per cent were polynuclear, were found. No organisms were seen on smear. On standing, the fluid showed a definite pellicle. The Pandy reaction was positive. The sugar was 55 mgs. per cent; chlorides were 690 mgs. per cent; protein 69 mg. per cent.

A blood count was as follows: hemoglobin, 80 per cent; red blood cells, 4,460,000; white blood cells, 14,200; polymorphonuclears segmented, 61 per cent; polymorphonuclears non segmented, 13 per cent; myelocytes, 1 per cent; plasma cells, 1 per cent; monocytes, 7 per cent; lymphocytes, 17 per cent.

A blood culture was taken and was later reported positive for H. influenzae. An intravenous drip was started with 5 per cent glucose in saline solution. To this 0.8 per cent sulfanilamide was added in sufficient quantity to total 0.2 Gm. per kilo per 24 hours. The child was extremely restless, tossing about, crying out about headache and urinating involuntarily. The temperature rose to 105 degrees.

Since no organisms had been obtained, it was thought that the condition might be a meningitis secondary to a nasal sinus infection. Dr. Samuel Rosen was asked

to see the patient. He obtained smears from the ethmoid sinuses which showed epithelial cells, a few pus cells, a few Gram positive cocci and diplococci, and Gram-negative bacilli which failed to grow on culture. Another lumbar puncture showed the same findings as the previous one.

It was decided to continue the sulfanilamide and glucose and to await the result of the bacteriological findings.

Late in the morning of December 17, the cerebrospinal fluids from the very first lumbar puncture and the one done in the hospital were both reported to contain influenza bacilli. On account of the nasal findings it was decided that the ethmoid and sphenoids should be laid open. This was done by Dr. Rosen, the child receiving nitrous oxide and oxygen anaesthesia. She made a good post operative recovery and was given a blood transfusion of 300 cc. of citrated blood.

The sulfanilamide was stopped and sulfapyridine was substituted, 0.6 per cent in 10 per cent glucose being given by vein, or a total of 0.2 Gm. per kilo per day.

Sixty cc. of anti-influenzal serum obtained from the New York City Board of Health was given intravenously.

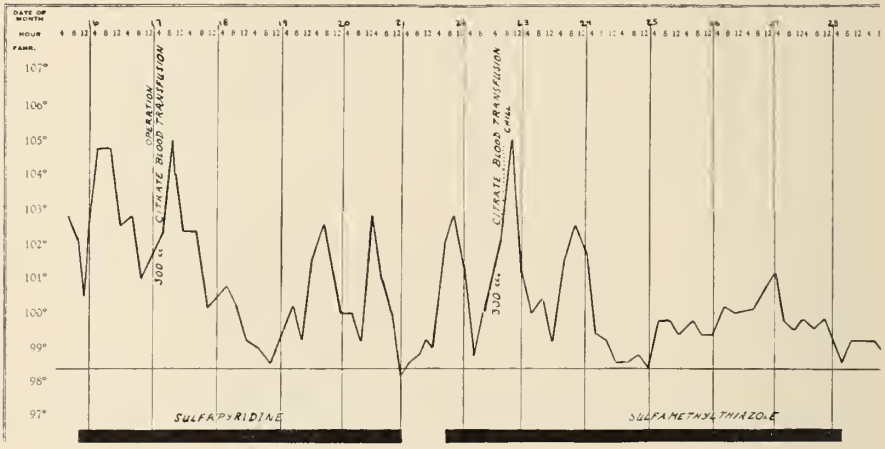

Fig. 1. Temperature Record

After this the condition of the child fluctuated. At times she was very violent and irritable; for several days she refused anything by mouth. Lumbar punctures were done daily, anti-influenzal serum being injected intraspinally each day for nine days, together with 10 cc. of 2 per cent sodium sulfapyridine solution.

On December 18th, the temperature fell rather abruptly from 105.2 degrees to 98.8 degrees and the child seemed definitely improved. The child was much brighter and began to take fluids by mouth during December 19th and 20th. On December 21st, gross hematuria appeared. Many red blood cells and sulfapyridine crystals were found in the urine. Sulfapyridine was stopped and sulfanilamide substituted by mouth. Forty-five grains were given in twelve hours. Lumbar puncture revealed only a few cc. of cloudy cerebrospinal fluid under very low pressure. The culture was reported negative as were all those subsequently obtained.

On December 22nd, several attempts at lumbar puncture proved unsuccessful and a "dry tap" was suspected. On this day, severe serum sickness appeared with urticaria and joint pains. Ninety grains of sulfanilamide per os were given during the day. On this evening sulfamethylthiozole was put at our disposal by Dr. Jose-

phine Neal who had seen the patient in consultation. This drug was given in place of sulfanilamide until January 3rd (see chart). On account of the great restlessness of the child, lumbar puncture was very difficult. It was, therefore, decided to perform lumbar puncture under general anaesthesia.

On December 23rd, 20 cc. of clear cerebrospinal fluid was obtained; it contained 370 cells. A blood transfusion of 300 cc. was given. A mild left sided facial paresis made its appearance but the general condition was greatly improved. The child was rational and took food well. The neck was much less rigid.

On December 24th, 25th and 29th, lumbar punctures were performed daily under anaesthesia, clear cerebrospinal fluid being obtained. The fluid of the last puncture showed no cells whatever under the microscope.

On January 1st, the temperature rose to 101.8 degrees and the child complained of joint pains which were considered due to serum reaction. Sulfamethylthiazole which had been stopped was again started and continued until the 4th of January. From then on improvement was rapid. Just before leaving the hospital on January 11th, a circinate erythematous eruption appeared over the body, most marked on the anterior chest. The eruption did not itch and did not involve the mucous membranes. It was interpreted as a serum or drug reaction.

When the patient left the hospital she was in very good general condition. She had no evidence of any residual neurologic condition. The facial weakness had disappeared. Her urine was normal.

Three weeks after leaving the hospital, a communication from her mother informed us that the child was perfectly well and had completely recovered from her illness.

DISCUSSION

It is evident that we were dealing with a severe type of infection. The child's temperature was over 104 degrees on the first night of her illness. She rapidly became comatose and remained so for several days. The blood culture was positive for H. influenzae as were the daily spinal taps from December 17th to December 21st.

One of the points of interest in this case is the question of surgical intervention. It was felt that one could not disregard the extremely foul odor from the nose which had been noted for about a week before the onset of the meningitis. In spite of the fact that influenzal meningitis in childhood is usually a primary disease, on account of the finding of pus in the sphenoids, it was decided to open both the ethmoid and sphenoid sinuses. Whether this procedure aided in the child's recovery, it is impossible to state. One certain fact is that immediately after the operation the fetor disappeared and never returned.

As stated previously, in treated influenza meningitis one may now look for recovery in about 50 per cent of the cases. There must be many, as yet unknown, factors involved in deciding the outcome of this disease since other cases treated in similar fashion have succumbed. Favorable factors were: (1) early diagnosis and treatment; (2) the possibility of having eradicated a focus by operating on the nasal sinuses; (3) the age of the child.

In regard to this last factor, Fothergill has called attention to several

interesting points. Influenzal meningitis is extremely rare in the first two months of life and is very uncommon after childhood. According to Fothergill (12) about 85 per cent of all cases occur between the ages of two months and three years of age. He pointed out that the blood of normal adults possesses a marked bactericidal power for meningitic strains of the influenza bacillus, but that the blood of individuals between the ages of two months and three years rarely shows this power. He says "With advance in age beyond this period, the bloods of an increasing percentage of children were found to exhibit bactericidal activity." This child at the age of eight may therefore have had some natural defense mechanism in her blood.

Record of blood examinations showing the effect of sulfamethylthiazole on the leucocyte count

DATE	R.B.C.	H.G.B. %	W.B.C.	POLYNUCLEAR NEUT.		LYMPHOCYTES	MONOCYTES	MYELOCYTES	PLASMA CELLS	EOSINOPHILES
				Seg.	Non-seg.					
12/16/39	4,460,000	80	14,200	61	13	17	7	1	1	
12/18/39	4,250,000	85	13,100	67	12	13	8			
12/20/39	4,260,000	80	13,050	54	14	17	7	2	1	3
12/22/39	4,130,000	75	22,600	72	10	10	8			
12/26/39	4,300,000	82	9,800	70	6	22	2			
12/28/39	4,300,000	77	8,200	61	8	31				
12/30/39	4,360,000	76	10,000	50	6	33	6			
1/ 2/40			5,000	67	5	18	6		1	3
1/ 3/40			4,100	44	4	34	13		2	3
1/ 4/40	4,520,000	88	4,300	43		44	8		2	3
1/ 6/40	4,330,000	83	3,400	42	6	39	12		1	
1/ 8/40	4,350,000	83	5,000	49	6	30	10			5
1/ 9/40	4,500,000	84	5,500	43		42	8		2	5
1/10/40	4,980,000	88	7,700	61	3	27	4	1	1	3
1/11/40	4,400,000	85	9,600	64	4	30	1			1

The role played by chemotherapy is hard to evaluate. As mentioned before, a few cases have recovered with chemotherapy alone. Of interest here is the fact that sulfapyridine was given for three days intravenously and then for two days by mouth, a total of 26.0 Gm. After this dosage hematuria with sulfapyridine crystals in the urine made its appearance. Sulfanilamide was substituted for a day followed by sulfamethylthiazole, of which 48 Gm. were given. It is interesting to study this dosage in relation to the white cells of the blood. The sulfamethylthiazole was started on December 26th when the blood count showed 22,600 leucocytes with 82 per cent polynuclear cells. Following this, the white blood cells fell until January 6th when they reached 3,400 with 48 per cent polynuclear neutrophiles. After this there was a rise to 5,000, 7,000 and finally to 9,200 with 64 per cent polynuclear cells, at the time of dis-

charge. Apparently there is the same danger of causing a leukopenia with sulfamethylthiazole as there is with sulfanilamide or sulfapyridine.

SUMMARY

A case of meningitis due to the H. influenzae is reported in a girl aged eight years. The child recovered. The records show that this is the only recovered case of this disease in the seventeen proved cases that have been treated in the medical wards at The Mount Sinai Hospital in the past ten years. Therapy consisted of intravenous and intrathecal anti-influenzal horse serum; sulfapyridine and later sulfamethylthiazole; continuous intravenous drip; daily lumbar punctures and two blood transfusions.

Recent progress in the therapy of influenzal meningitis is discussed.

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CORONARY INSUFFICIENCY AND MYOCARDIAL NECROSIS DUE TO ACUTE HEMORRHAGE

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The condition of the cardiac muscle, and therefore, the electrocardiogram, depend on the circulation to the heart, that is, the coronary blood flow. Changes in the latter have generally been associated with organic involvement of the coronary arteries, particularly coronary artery occlusion with infarction of the muscle. Yet a similar alteration may result from coronary insufficiency due to other causes, such as aortic stenosis (1), shock, and pulmonary embolism (2). These produce anoxemia and impaired nutrition of the heart which may result in areas of necrosis. In turn, there may be significant changes in the electrocardiogram. In this report we wish to point out that a sudden loss of blood, for example, from the gastrointestinal tract, may have the same effect upon the heart. The changes are more apt to occur when coronary disease is present but may be manifest in its absence. This is so even in young persons, as the following case demonstrates.

CASE REPORT

History (T. L., Adm. 428453). This young woman of 19 became pregnant five months before admission. Two months later a bloody diarrhea set in, with six stools daily, and fever. Sulphanilamide was administered without effect. Two weeks before admission the temperature reached 106°F. and the patient aborted spontaneously. Her condition grew more serious, the temperature being 106°F., and on admission the patient was stuporous.

Examination. There was extreme pallor of the skin and mucous membranes. Numerous hemorrhages were present in the retina. The heart was not enlarged but a number of murmurs were present, the loudest being systolic and diastolic over the aortic area. These were considered to be hemic in origin. The pulse was Corrigan in type and the blood pressure was 130 systolic and zero (?) diastolic on one occasion.

Laboratory Data. There was a very severe anemia; 19 per cent hemoglobin and 1,000,000 red blood cells were present. There were 20 normoblasts and 2 erythroblasts per 100 white blood cells. The latter numbered 19,000 (51 per cent polymorphonuclear neutrophiles; 46 per cent lymphocytes). There were 320,000 platelets. Sternal puncture revealed that the bone marrow was very cellular with a marked increase in normoblastic activity. The blood culture was negative. The blood urea was 49 mg. per 100 cc. of blood. The electrocardiogram (Fig. 1) revealed depression of the RS-T segment and low T-waves in the three standard leads and in the chest lead, indicating myocardial damage.

Course. The diagnosis was ulcerative colitis with massive hemorrhage, severe

secondary anemia, and sulphanilamide intoxication. Her condition went rapidly downhill. The temperature varied between 103° and 104°F.; slight icterus appeared. A bilateral peripheral neuritis developed. Continuous transfusion was administered but the intestinal bleeding continued and the patient died eight days after admission.

At necropsy the entire colon and ileum were involved by acute ulcerative colitis; there were aspiration hemorrhagic bronchopneumonia of the upper and lower lobes of each lung and necrosis of the anterior and posterior papillary muscles. The coronary arteries were normal.

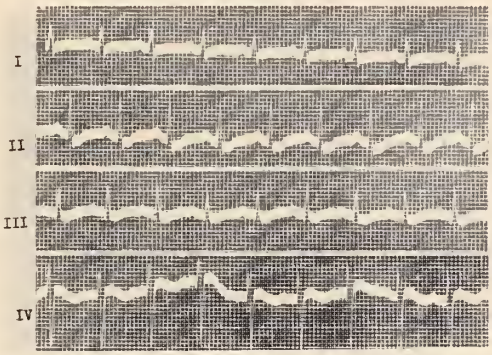

FIG. 1. The electrocardiogram shows depression of the RS-T interval in the three standard leads, and low T-waves in all four leads. In the absence of digitalis, these changes indicate myocardial involvement.

DISCUSSION

The RT and T-wave abnormalities in the electrocardiogram of this patient indicated that the heart muscle was acutely damaged and this was confirmed at the post mortem examination. There was infarction of the papillary muscles, similar to that seen following acute coronary artery occlusion, although the coronary arteries were not at all affected. In this case the alterations in the myocardium may have been caused by the anemia, the infection or, conceivably, by the administration of sulphanilamide. That the latter affects the heart has not been demonstrated; in several cases studied thus far no changes were noted. The role of ulcerative colitis in the production of the cardiac changes can also be excluded as significant, for we have shown that it does not alter the electrocardiogram (3). Furthermore, infection is associated with diffuse inflammatory changes in the myocardium and not with necrosis limited to the papillary muscles. The latter is characteristic of interference with the coronary circulation and in the case reported must be attributed to the extreme anemia of rapid onset. The diminished oxygen-carrying capacity of the blood was sufficient to produce coronary insufficiency with severe anoxemia of the cardiac muscle even in the presence of normal coronary arteries. Coronary insufficiency may also be present in chronic anemia and may induce an anginal syndrome. We have found that changes may appear in the electrocardiogram if the hemoglobin falls below 25 per cent (4).

This case demonstrates that myocardial infarction may occur without occlusion of a coronary artery and may present a problem in differential diagnosis, clinically and electrocardiographically. It is our impression, however, that the majority of such cases present few or no symptoms referable to the cardiac damage. The electrocardiogram also differs, as a rule, from the typical pattern observed in coronary occlusion in that there is depression of the RS-T segment and absence of Q-waves in coronary insufficiency.

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A POSSIBLE RELATIONSHIP BETWEEN THE DUCTLESS GLANDS SECRETING THE SEX HORMONES AND PEPTIC ULCER*

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Certain clinical observations suggest that the ductless glands, particularly those involved in the sex cycle, play a rôle in the problem of peptic ulcer. For example, it is well-known that during pregnancy ulcer symptoms frequently improve or disappear. Also, there appears to be a fairly large group of patients who, at the natural or artificial menopause, experience the onset or exacerbation of a peptic ulcer. Furthermore, peptic ulcer is strikingly predominant in the male sex. When it occurs in women, it is comparatively a mild disease. Perforation, hemorrhage, and postoperative recurrent ulcers are quite infrequent in women.

There is also some experimental data which appears to have a bearing on the problem. The late Eugene Klein, working in the laboratory of this hospital, found that during lactation in dogs the acid secretion from abdominal wall fundus pouches increases markedly and that abdominal wall ulcerations occurring about the orifices of the pouches enlarge considerably (1). Franklin Hollander also noted that the secretion from Pavlov pouches increased several times in amount during lactation (2). I next observed that during estrus in the dog the secretion from a fundus pouch diminished markedly and the ulcerations about the pouch healed completely (3).

Translated in terms of the ductless glands secreting the sex hormones, these experimental observations indicate that the anterior pituitary gland (which secretes the lactogenic hormone) may be associated with the increased secretion and ulceration, whereas estrin, possibly with progesterone (causing estrus), is involved in the healing process during the estrus. The possible relationship of such abdominal wall ulcerations to internal gastroduodenal ulcer should be considered.

In view of the fact that estrin is inhibitory to the anterior pituitary gland, it is tempting to argue that the mildness and infrequency of the ulcer disease in women may be the result of normal pituitary inhibition by estrin, and thus it is possible to hypothecate that peptic ulcer is primarily a pituitary disease in which some increased anterior pituitary secretion leads to peptic ulcer. Androgen and estrin plus progesterone may normally check this hyperactivity. An imbalance may lead to peptic ulcer.

* Read at the Annual Graduate Fortnight of the Academy of Medicine in the Blumenthal Auditorium, The Mount Sinai Hospital, October, 1939.

The best example of an unchecked, uninhibited, or hyperactive anterior pituitary gland is found during the menopause. Here, of course, estrin and its inhibitory influence on the pituitary is almost completely absent. Therefore, among other approaches to this "ductless gland-peptic ulcer" question, we have studied the relation of peptic ulcer or ulcer-like symptoms to the natural or artificial menopause in patients. We have been quite impressed by the frequency with which we encountered the onset of ulcer or ulcer-like symptoms at the time of the menopause. Also, if the patient had had a peptic ulcer there was often a marked exacerbation of her symptoms at the onset of the menopause. Another group commenced some time after the menopause. It is noteworthy that the severe ulcer complications in women seem to occur at or after the menopause. In view of the small total number of female ulcer patients encountered on the wards and in the Gastro-intestinal Clinic of our hospital, the large percentage of cases which had an apparent relationship of the ulcer symptoms to the menopause is quite striking.

We saw in our Gastro-intestinal Clinic in a recent five-year period, 540 cases of peptic ulcer. Ninety (or 1 in 6) were females. Of these, 40 or 44 per cent experienced the onset of their ulcer symptoms at the menopause (natural or artificial).

Obviously, the next step was to determine the influence of estrogen therapy on this group of patients. Twenty cases were selected in whom the ulcer symptoms started coincidentally with the onset of an artificial or natural menopause. Test meals and radiographs were taken before therapy was instituted. This part of the investigation was carried out in cooperation with Dr. U. J. Salmon in the Menopause Clinic of Dr. S. Geist. These twenty patients received estrogen in the form of 20,000 international units of Progynon B., intramuscularly, three times a week for a period of three weeks. The vaginal epithelium was studied in order to ascertain if the dosage was effective. In some cases a weekly gastric analysis was carried out. In others a test meal before and at the end of the period of therapy was given. We were impressed by the symptomatic improvement during this type of treatment. There was no notable change in most of the acidity curves. A few cases showed a striking reduction. In some patients the clinical improvement persisted for some months. Recurrences were frequent but were usually quickly relieved by further injections of the hormone. In addition to the relief of the ulcer symptoms, the usual nervous symptoms of the menopause (insomnia, dizziness, flushes, constipation) were also benefited.

Whether the improvement noted in this group of cases after estrogen therapy is attributable to a specific effect on the gastric function or mucosa *per se* or whether it is a secondary effect brought about by a general symptomatic improvement, that is, relief of the neurovascular symptoms of the menopause, remains an open question. The fact remains that

ulcer or ulcer-like symptoms at or about the menopause may be relieved in the majority of cases with estrogen therapy.

While we hesitate to draw a conclusion from this limited number of cases, we feel that this form of substitution therapy is worthy of a trial. The use of androgen, estrogen and progesterone in the treatment of peptic ulcer both in females and in males awaits further experimental and clinical investigations. It is realized that the clinical and experimental observations mentioned herein require confirmation and extensive study before conclusions concerning the possible relation of the ductless glands to peptic ulcer are drawn.

SUMMARY

(1) The infrequency and mildness of peptic ulcer in the female may be due to a ductless glandular factor.

(2) The clinical and experimental observations cited in the text suggest that an unchecked or hyperactive anterior pituitary gland may be the factor.

(3) The high incidence of peptic ulcer at and after both the natural and the artificial menopause suggests a relationship to the anterior pituitary gland.

(4) On the possible basis of a hyper-pituitarism, estrogen therapy is suggested for inhibition purposes.

(5) In a small group of patients in whom ulcer appeared at the menopause estrogen therapy was instituted with good results.

(6) The possibility of extending these studies to the use of estrogen, progesterone, and androgen in the study and therapy of peptic ulcer generally, is tentatively suggested.

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ACUTE INTESTINAL OBSTRUCTION WITHOUT ROENTGENOGRAPHIC EVIDENCE

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The value of roentgenography in the diagnosis of intestinal obstruction has been known for many years. Following the pioneer work of Schwarz (17), Case (3), Stierlin (20), and others, X-ray examination of the abdomen without the use of contrast media in acute intestinal obstruction has become routine in all large clinics. It is the purpose of this report to present a proved case of typical acute intestinal obstruction in which the roentgenogram of the abdomen did not reveal dilated small bowel.

CASE REPORT

History (Adm. 436033) N. K., male, 50 years old, was admitted to The Mount Sinai Hospital on February 8, 1939. His chief complaint was abdominal pain of six hours' duration.

Appendectomy was performed twenty-four years before admission for an attack of acute appendicitis. A diseased appendix was removed and the wound drained. Four weeks after operation all drains were out and the wound was healed. Abdominal symptoms developed in apparent relationship to the operation. There was complaint of "heartburn" and constipation. Because of the persistence of the former symptom, a gastro-intestinal X-ray series was done eight years before admission. The report was negative for organic disease. About six months before entry to the hospital, he began to suffer from mild transitory attacks of "cramps" situated below and to the left of the umbilicus. These pains were not related to meals and were usually relieved by a bowel movement or passage of flatus. Two months after the onset of these attacks, extremely loud borborygmi were noted. His pains increased in severity and frequency, and the rumbling became more marked, especially after the ingestion of food. Constipation which required frequent enemata remained unaltered. During the attacks of pain, abdominal distention occurred which was sufficiently severe to require loosening of the clothes. Bicarbonate of soda often relieved the distention.

At ten o'clock on the morning of admission, there was an attack of severe cramplike pain with slight abdominal distention. Bicarbonate of soda was of no avail. Four hours later a tap water enema was given which resulted in a clear return, some flatus, but very little relief from pain. A hot tub bath was taken but the cramps continued unabated. During this period the patient was nauseated but did not vomit. About five hours after the onset of pain, the patient came under observation.

Examination. He was acutely ill and complained of severe, generalized, cramplike, abdominal pain, most marked in the lower abdomen. Heart and lungs showed no abnormality. The remainder of his general examination was normal. The abdomen, which was thick-walled, was somewhat distended but no visible or palpable peristalsis was present. Diffuse moderate tenderness with some voluntary rigidity to palpation could be elicited. There was a well-healed broad scar in the right

lower quadrant. Hernial orifices were negative. Rectal examination revealed no pathology.

X-ray examination was performed six hours after the onset of symptoms. The report was as follows: "A preliminary film of the abdomen showed no distention of the large bowel. The small bowel showed a small amount of gas which was not characteristic of obstruction. Barium enema examination failed to show an obstruction to the passage of barium from the rectum to the cecum. The lumen of the colon could be filled completely. The sigmoid swung well over to the right and was fixed in the region of the caput coli. On the films, however, the distal sigmoid, as it swings to the right, is compressed and narrowed uniformly. The mucosal pattern is shown and appears normal." For this reason it was thought that there existed an intrinsic mass compressing the sigmoid.

When this report was received the patient was given Magendie solution min. VII (morphine 0.015) for the relief of pain. An ox-gall enema at 5:20 P.M. resulted in the return of much flatus and some fecal particles. Post evacuation X-ray examination showed practically complete retention of barium, with the same deformity of the sigmoid. The enema and morphine gave some relief and further observation was decided upon. During the night abdominal pain recurred, in spite of a rectal tube, codeine, and a low enema. The following morning, twenty-five hours after the onset of illness, operation was decided upon. Preoperative diagnosis was acute intestinal obstruction due to previous laparotomy adhesions.

Operation. (Anesthesia: Procaine 150 mg. intraspinally supplemented by nitrous oxide-oxygen-ether inhalation). The abdomen was opened through a liberal lower left rectus muscle-splitting incision. There was present a moderate amount of serosanguinous fluid in the peritoneal cavity. Several loops of small bowel presented which were distended with fluid and gas. An adhesion was present between the sigmoid and cecum pulling the former over to the region of the old abdominal scar. A loop of small intestine was also adherent at this site. Palpation revealed a partially fibrous ring which was formed by the sigmoid above, the posterior parietal peritoneum below, the cecum mesially and the sigmoid and meso-sigmoid laterally. When this ring was dilated manually a loop of distended small intestine, which had prolapsed into this space, was freed. The intestine distal to this stricture caused by the ring-like formation was collapsed. The loop of obstructed intestine was about twelve inches in length, dilated to about two and one-half times the normal diameter, and was markedly edematous. It contained fluid and gas and the serosal surface was reddish-purple in color and lacked lustre. When the obstruction was relieved, the collapsed bowel immediately filled. The adhesions between the sigmoid, cecum, and cicatrix of the abdominal wall were severed, as well as the adhesions to the small bowel. A few serosal sutures were employed to cover the bare area on the small intestine where the adhesion had been attached. The abdomen was closed in layers without drainage.

Postoperative Course. For the first week frequent enemata and colonic irrigations were necessary for the relief of abdominal distention. Heartburn, which had been present for many years, was treated by continuous milk drip with marked improvement. X-ray examination of the abdomen, shortly before discharge, showed no evidence of intestinal obstruction. Barium enema showed a normal colon. The previously described deformity and fixation of the sigmoid was no longer present. The extrinsic mass postulated preoperatively was undoubtedly the dilated loop of obstructed intestine which caused the deformity of the sigmoid visualized on the barium enema. At the time of discharge, on the sixteenth postoperative day, the patient was symptom-free on a second week Sippy diet. There have been no symptoms of intestinal obstruction.

DISCUSSION

It is generally agreed that roentgen examination of the abdomen is of great value in the diagnosis of acute intestinal obstruction. A voluminous literature has accumulated in the past twenty-eight years consisting of case reports and series of cases in which roentgenography by "flat plates" has been employed. The experimental work by Ochsner (10), Wangensteen (22), Swenson and Hibbard (21), and others has shown that intestinal obstruction can be recognized in roentgenograms at a very early stage (2–6 hours). Numerous clinical observers have reported series of cases in which roentgenography either corroborated or ruled out a diagnosis of intestinal obstruction. Causes for error, such as the use of cathartics or cleansing enemas and the presence of gas in the small intestine of debilitated or very young patients, have all been mentioned. Buckstein and Michaels (2), Rendich and Abrams (15), and others list numerous conditions which may simulate the X-ray findings in acute intestinal obstruction. All authors except Darrow (6) stress the great value of this adjuvant in the diagnosis of intestinal obstruction, but very few mention its shortcomings. Quist (14) states that "obstruction cannot be excluded even though no gas is seen in the small intestine on X-ray film." Patey (12) mentions a case of post-appendectomy ileal obstruction in which the X-ray diagnosis was not made. He mentions the difficulty of interpretation of the plates in ileal obstruction. Chapman (5) analyzed a large series of cases and came to the conclusion that in 80 per cent of the cases correct diagnoses can be made. In reference to negative diagnoses, he stated that they are correct in 79 per cent and incorrect in 21 per cent in his series. These are the only references to proved cases of intestinal obstruction in which the X-ray films failed to reveal pathognomonic evidence, such as small bowel gaseous distention, fluid levels, or step-ladder patterns. The case herein presented was one of proved acute small bowel intestinal obstruction. Enough time (six hours) elapsed to allow a positive roentgen diagnosis to be made. The "flat plate" failed to reveal any signs of small bowel intestinal obstruction. The argument that an upright film should have been taken may be advanced. However, although it is true that fluid levels are better visualized in the upright posture, flat plates are of greater value in demonstrating gaseous distention. In addition, the distribution of the gaseous distention, which is important in the determination of the level of the obstruction, is better observed in the prone position. Case (3) advocated the use of a plate under the abdomen with the patient in bed. He used a portable machine and claimed excellent results. Other authors stress the importance of the presence of gaseous distention in the diagnosis, and claim that this sign is more constant and appears earlier than do fluid levels.

SUMMARY

1. The absence of roentgenographic evidence of obstruction of the small intestine does not exclude the presence of acute intestinal obstruction.

2. A survey of the literature reveals emphasis on the value of roentgenography in the diagnosis of acute intestinal obstruction, with little reference to the occurrence of negative films in proved intestinal obstruction.

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BACTEREMIA OF OTITIC ORIGIN

Report of Case Presenting Problem in Diagnosis; Recovery Following Unusually Complicated Course

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Of all otitic complications, thrombosis of the sigmoid sinus is probably the one most closely related to internal medicine and to the various specialties. Perhaps in no other otitic disease are the services of these specialists so frequently requested to aid in the solution of the many diagnostic problems and in the treatment of the complications that arise in the course of the illness. This is strikingly illustrated in the case herein presented in which the final recovery of the patient must be attributed to the combined efforts of the pediatrician, orthopedist, internist, neurologist, surgeon, hematologist and roentgenologist, besides those of the otologist.

CASE REPORT

History (Adm. 448465). D. B., a boy 5 years of age, was admitted to the otologic service of Dr. Maybaum on May 30, 1938, with a history of cervical adenitis for fourteen days, pain in the left ear for ten days, and spontaneous discharge from the ear for seven days. The ear discharge continued up to time of admission. Within the twenty-four to thirty hours before admission the child vomited, had two chills and his temperature was 105°F. The past history was irrelevant.

Examination. The child was extremely toxic and flushed, appearing gravely ill. There was marked congestion of the nasal and pharyngeal mucosa, and râles were heard in the chest. The cervical glands were enlarged. Signs of meningeal irritation, i.e., bilateral ankle clonus, hyperreflexia, and nuchal spasticity, were elicited. The spleen and liver were enlarged, the former three and a half fingers and the latter one finger below the costal margin. The fundi were negative.

Ears. There was an active pulsating purulent discharge from the left ear which reappeared readily after wiping. Tenderness was present over the mastoid. The right ear was normal.

Laboratory Data. Blood count revealed a leukocytosis of 17,400 with 4,400,000 red blood cells and hemoglobin of 70 per cent. The urine contained glycogen and bile. X-ray examination of the left mastoid disclosed a diffuse haziness over the entire bone with an area of destruction in the tip. X-ray examination of the chest disclosed no evidence of pneumonia.

Course. From the history and physical signs the diagnosis of acute mastoiditis with otitic sepsis was strongly suspected. A simple mastoidectomy was performed which revealed extensive destruction of bone. The wall of the sigmoid sinus, exposed for visualization, appeared normal. Culture of pus from the mastoid yielded Streptococcus hemolyticus.

The two blood cultures, one taken on the day of admission and the second, three days later, were sterile. On the fourth day the patient developed a metastatic focus in the left hip. This constituted sufficient clinical evidence to establish the diagnosis of otitic sepsis and to warrant obliteration of the sigmoid sinus and ligation of the jugular vein, in spite of the two previous negative blood cultures. At operation phlebitis of the parietal wall of the sigmoid sinus was observed but when the vein was incised free bleeding was encountered from the jugular, as well as from the torcular, end.

The leg was placed in traction by the orthopedist. Citrate transfusions and intravenous saline were administered to combat the low hemoglobin content of the blood (40%). In spite of these measures the child continued to be critically ill, the septic temperature having persisted and abdominal distension, cyanosis, hyperpnea and tachycardia having set in. The third blood culture, taken one week after admission (three days after operation), was the first culture to be reported positive for Streptococcus hemolyticus.

The administration of sulphanilamide effected a slight improvement in the child's condition for the next week. At the end of this time, however, there appeared a puffy, pitting edema of the skin and excessive perspiration. Because of these signs, together with the tachycardia and abdominal distension previously mentioned, and because of the high carbohydrate diet, the diagnosis of vitamin B deficiency was made. This condition responded very favorably to the administration of vitamins B and C.

On the twenty-seventh day in the hospital, a blood count, taken by Dr. Rosenthal, disclosed a typical picture of agranulocytosis; white blood cells, 1700, (lymphocytes, 89 per cent; polymorphonuclear leukocytes, 8 per cent). The agranulocytosis was naturally ascribed to the sulphanilamide which had been administered for nineteen days in doses averaging 130 grains daily. This drug was immediately discontinued and four daily transfusions were given to combat the degeneration of leukocytes, with excellent results.

Because of the continued unexplained septic temperature, nuchal rigidity, and the poor condition of the patient, re-exploration of the sigmoid sinus was undertaken. The operative findings were essentially negative, no clue being found to account for the symptoms. The cause for the septic temperature was subsequently disclosed, however, when, on aspiration of the left hip joint, thick purulent exudate was obtained. Streptococcus hemolyticus was cultured from the pus. A huge boggy swelling in the left lateral pharyngeal wall, which was incised with the evacuation of thick creamy pus, accounted for the nuchal rigidity. Following these procedures the child showed signs of improvement but the presence of organisms in the blood stream persisted. After repeated transfusions the blood gradually became sterile and the local wounds healed satisfactorily. Under the care of the orthopedic service, to which the child was later transferred, a very good result with regard to motion of the hip was obtained. He was discharged from the hospital on December 9, 1938, about six and a half months after admission.

COMMENT

Many interesting clinical features are presented in this case. Of these, the difficulty in establishing a diagnosis is outstanding. Though an otitic sepsis was strongly suspected early in the disease the diagnosis was not established until a metastatic focus in the hip subsequently appeared, two blood cultures in the interim having been sterile. As a rule, at The Mount Sinai Hospital blood cultures have been of inestimable value in

the diagnosis of otitic sepsis. With the excellent culture media and technique employed, the organism was recovered very early from the blood stream in about 90 per cent of the cases. In this case the Streptococcus hemolyticus was first recovered from the blood three days after operation on the sigmoid sinus. Of further interest is the fact that once the bacteremia appeared it persisted for a period of at least forty-one days. During this time re-exploration of the sigmoid sinus was undertaken to disclose, if possible, an explanation for this condition but the operative findings were negative. Subsequent incision and drainage of the metastatic focus in the hip revealed the cause for the continued sepsis.

The parapharyngeal abscess was undoubtedly the result of an extension from the infection in the neck at the site of the jugular ligation.

The agranulocytosis, an untoward complication of the sulphanilamide therapy was the cause of considerable concern. It appeared at the end of nineteen days after the drug had been started, during which time the patient had received about 130 grains daily or a total of 1,470 grains. As is well known, agranulocytosis is a serious complication proving fatal in more than 50 per cent of the cases. Fortunately, in this instance, the immediate discontinuance of the drug and the administration of blood transfusions brought about a rapid regeneration of the white blood cells.

Finally, in reviewing this case from the economic standpoint it is to be observed that during the prolonged course of the illness, namely a period of six and a half months, the patient underwent four major operations and received sixteen transfusions totalling 4,350 cc. of blood. In addition, nine blood cultures and other innumerable laboratory and therapeutic measures were performed.

SELECTED TOPICS IN TOXICOLOGY*

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Poisoning was chosen as the theme of my lectures although the majority of you are not in great need of a "brushing up" of your knowledge of this subject for I am well aware that cases of poisoning are not too frequent at your hospital. Moreover, in private practice the occasion and necessity for treating poisoning in patients is also rather rare. There are, however, two reasons why I chose to bore you a little with a discussion of some organic and inorganic poisons. First, there are in this great community in which we are living, many who are threatened daily and at every hour of the day and night by known and unknown poisons. It is a fair guess that a great number of instances of poisoning are not being recognized as such and that such individuals do not receive the proper treatment in the early, and the more important, stage of the disease. Zangger, professor of legal medicine in Zurich, estimates that only 20 per cent of all cases of poisoning are recognized as such. I dare not venture an opinion as to whether in this country such a high rate as 80 per cent of the cases escape the right diagnosis. But even a much lower rate of incorrect diagnosis in cases of poisoning might warrant drawing attention to some of the drugs which can menace human life. The second reason for my choice was the fact that toxicology is but an integral part of Applied Pharmacology, for actually there does not exist a fundamental difference between drugs that heal and drugs that kill. All remedies which act in the animal or human body are essentially poisons, since their clinical action in the body or their influence on the metabolism, whether beneficial or noxious, depends only on the various conditions of the organism and on the dose of the administered drug.

THE VARIABILITY IN SENSITIVITY TO DRUGS

There are many instances in which the effect of a given drug changes with the individual, often without our knowledge of the cause. You are all familiar with the alleged, and possibly real, dangers of *pyramidon* and the resultant agranulocytosis in some sensitive persons living in countries situated near the sea in the northern hemisphere, while people living inland on the continent of Europe seldom show a sensitivity to pyramidon and even

* The first of a series of lectures introducing discussion of selected topics in toxicology, delivered before The Mount Sinai Hospital Staff during January and February, 1940.

doses of several grams of this drug can be taken daily without causing any harm for a long period of time. Another striking example is the individual variation of sensitivity to atropine. This sensitivity is at its minimum in childhood and senility; it becomes greater in adolescence, when the "tonus" of the vagal nerve has its greatest sensitivity to atropine. The sensitivity to opium and morphine behaves, as is well known, in a directly opposite manner; it is highest especially in early childhood. On the other hand, it is obvious that various diseases change to a large extent the effect of one and the same remedy. It may be recalled that antipyretics do not influence at all the temperature of a normal and healthy animal or human body, whereas in fever the organism shows particular sensitivity to antipyretics, which can lower the temperature and bring it down to the normal level. Extreme changes of sensitivity to many remedies and poisons occur in hyperthyroidism. You are aware of the dangers of iodide administration in some cases of this disease and, on the other hand, with the complete inactivity of digitalis preparations in their effect on the hearts of patients with Graves' disease. I want to remind you of the particularly high toxicity of *dinitrophenol*, the well-known remedy against obesity, when combined with thyroxin medication. The variability in sensitivity to drugs is best illustrated by the series of fatal accidents which occurred not long ago in this country; a pharmaceutical laboratory prepared a sulfanilamide solution, using ethylenglycol as a solvent, a liquid which usually shows no toxic effect. It happens that the organism under the influence of sulfanilamide becomes highly sensitive to different substances which are otherwise quite harmless in usual doses. This is so in the case of morphine, codeine, papaverin, and also ethylenglycol. This sensitivity to *ethylenglycol* of the sulfanilamide rendered the harmless ethylenglycol highly toxic and all of the patients treated with this sulfanilamide solution were severely poisoned. Another striking example of change in toxicity is is offered by *cyanamid-calcium*, CN_2Ca. This compound is used as a fertilizer and sometimes poisons farmers working with it. The symptoms are headache, congestive hyperemia of the face and of the upper third of the body, increased heart action with lowering of the blood pressure, and a feeling of giddiness. The poisoning becomes, however, severe and appears, after otherwise harmless doses, if the farmers are under the influence of alcoholic drinks and the lowering of the body temperature induced by alcohol becomes greatly increased. Experiments show that *cyanamid* causes greater narcotic action of sodium bromide and the diuretic action of the theobromine. Another similar effect of alcohol has been observed for a long time in *aniline* factories, where workers who have been indulging excessively in alcoholic drinks on Sunday are particularly subject to aniline poisoning on the following Monday, since alcohol affects the oxygen supply necessary for normal metabolism. The noxious influence of alcohol is also traceable in cases of lead poisoning.

It is not necessary to remark that the action of drugs varies in different individuals and animals. The inactivity of atropine in rabbits and goats is highly interesting. It is produced by an enzyme destroying the atropine-ester. This enzyme is only in the blood and in the fluids of herbivora, but is not present in the human blood. Therefore, atropine acts on the human eye for several days or may remain active for a whole week. On the other hand, the homatropine, mandelic ester of tropine, is split up by an esterase of the human aqueous humour and acts, therefore, on the human iris for a short time only (S. Glaubach).

BEHAVIOR OF DRUGS IN ACCORDANCE WITH METHOD OF THEIR ADMINISTRATION

The toxic action of drugs is influenced and changed to a very large extent by the method of administration, as the rate of absorption is determined to a high degree by the properties of the mucous membranes, apart from other factors, such as solubility in water and lipoids.

Intravenous and intramuscular injection. The most effective method of administration is the intravenous injection. This is the usual means of administering substances which are expected to act quickly, such as strophantin in its effect on the weak heart. The sudden action of drugs on the heart and on the whole of the circulatory system, when injected intravenously, makes it imperative always to inject the drug slowly. Rapid injection leads nearly always to tragic results. This happens also in the intravenous injection of narcotics, causing sudden paralysis of the respiratory centers and that of the heart, if meticulous care is not taken to inject slowly. The intramuscular injection is close to the intravenous in its effects. The extensive capillary vascularisation makes the intramuscular injection always equivalent to the intravenous, and the doses of remedies for intramuscular application which have been adapted for the use in intravenous injection are almost the same as for intravenous injection.

Inhalation. Next to the resorptive power of muscle tissue is that of the respiratory tract. If you take into account that the total surface of the *alveoli* is nearly one hundred square meters and presents an exceptionally dense capillary network, then you will easily understand why the absorption of inhaled vapors, narcotics, or poisonous gases such as carbon monoxide or sulfur hydride, is so rapid. It must also be mentioned that this effect does not depend on the quantity but on the concentration of the inhaled gas, on the duration of the inhalation, and on the solubility of the gas in the blood. The greater the solubility of the gas in water or blood, the longer it takes for it to produce narcosis. Accordingly, the least soluble gases, *nitrous oxide* (N_2O) for instance, produce very rapid anesthesia when inhaled in sufficient concentration, whereas the water soluble ether takes a long time until a narcosis can be reached which is sufficient

for surgical needs (see table 1). The rapid saturation of blood with the less soluble gases like nitrous oxide and acetylen is, therefore, used in the determination of the cardiac output.

Another important site of quick resorption of poisons is the *nasal mucous membrane*. As you know, fatal cocaine poisoning occurs through absorption of cocaine applied to the nasal mucous membranes. Pituitrin is administered through the nasal mucous membrane in the treatment of diabetes insipidus for similar reasons. Fluids and solutions, likewise, when introduced into the bronchi are exceedingly quickly absorbed as in the case of water and physiological saline. Hypertonic saline, however, must be diluted in the lungs before absorption can take place. What quantity of lipoid soluble substances, as for instance lipiodol introduced for X-ray examination into the lungs, can be absorbed is not precisely known. The surprisingly rapid resorption of pulmonary edema and of pneumonic infiltrations gives impressive evidence of the adsorptive capacity of the lung surface.

Oral administration. Of great practical importance is, of course, the absorption of poisons through the digestive tract. As is well known, many

TABLE 1

Solubility and narcotic concentration

	ETHER	$CHCl_3$	CHLOR ETHYL	ACETYLENE	NITROUS OXIDE
Solubility factor	15	10	2.5	0.7	0.4
Narcotic concentration	4	1.3	4	80	100

substances are absorbed by the mucous membrane lining the mouth, such as atropine, cocaine, nitroglycerine, which are often used in *per lingual* administration. *Nicotine* and *prussic acid* dropped on the tongue produce severe symptoms of poisoning even after a few seconds. This easy absorption of poisons in the mouth is to be contrasted with the limited absorption power of the stomach. Only substances soluble in lipoids, like *ether, alcohol*, and *chloroform*, can be readily absorbed, and in a similar way *saline* and *sugar*. But the absorption can be considerably increased if the substances are dissolved in alcohol, or if they are allowed to remain for a longer time in the stomach by blocking the pylorus. Under such circumstances poisons which normally are not absorbed, such as *metrazol* or *hypnotics* like *evipan*, can be absorbed by the mucous membranes of the stomach. Ordinarily *alkaloids* can not be absorbed in the stomach. Experiments show that a frog whose pylorus has been blocked cannot be poisoned with strychnine or curare.

On the other hand, certain poisons are excreted by the mucous membrane of the stomach, such as morphine and, perhaps, mercuric chloride and sodium fluoride. In each case hydrochloric acid is of great importance in

the effect of the poisons introduced by mouth. Hydrochloric acid is not only a good disinfectant but it is sometimes able to liberate a poison. For example, barium sulfate may be contaminated with barium carbonate. In such event, the latter when acted upon by hydrochloric acid is converted into water soluble barium chloride, a substance which causes severe poisoning.

The absorbing activity of the *intestines* is very high but it also depends on the solubility of the poisons introduced. The resorbtion of fat-soluble substances, such as phosphorus or filix mas, is improved by the introduction of milk. Alkaloids, which are fixed in vegetable "ballast" substances, such as mucin or tannates, are absorbed very slowly. Therefore, it is useful, if a delayed action is desired, not to administer pure alkaloids like morphine, atropine, or strychnine, but their corresponding vegetable extracts, that is, *extractum belladonnae*, *opii* or *strychni*. In these extracts the alkaloids are fixed and need to be gradually liberated; when so administered they act steadily for longer periods.

Charcoal obtained from vegetable and animal material acts in a way similar to the function of these "ballast" substances in the vegetable extracts which fix the alkaloids chemically. The action of charcoal depends, of course, mainly on its large surface and is due to a physicochemical mechanism. This absorptive power of charcoal protects indirectly the mucous membranes of the gastro-intestinal tract. Charcoal is a very old and excellent remedy in the treatment of various poisonings. It has the ability of fixing electro-positive, as well as electro-negative substances and can be administered, suspended in water, in large doses. The basic advantage is, however, that charcoal has a very good adsorbtive power. This can be easily tested by decoloration of dyes, as for instance methylene blue (methylthionine) or by the adsorption of alkaloids such as strychnine. The good adsorptive power of charcoal is, perhaps, the best means of neutralizing inorganic and organic poisons in the gastro-intestinal tract. *One-tenth of a gram of charcoal with good adsorption power is sufficient to decolorate at least 20 cc. of a one-tenth per cent methylene blue solution. Carbo animalis, as dispensed by a pharmacy (bone charcoal), decolorates 2.3 cc., whereas Carbo ligni decolorates only 0.4 cc. A mixture called Universal Antidote, consisting of two parts Carbo ligni, one part each of magnesium oxide, and tannic acid decolorates 3.5 cc.* (see table 2).

A survey of the speed of resorption and the effects of poisons in oral, subcutaneous or intravenous administration is given in table 3. In oral administration an additional factor should be considered namely the decomposition by the digestive juice which diminishes the effect of poisons introduced in the gastro-intestinal tract. This is the case, for instance, in *K-Strophanthine*, which is destroyed in the stomach. That is why the *tinctura strophanthi* has no great effect.

Rectal administration. Finally, the rectum as a site for the absorption

of poisons must be considered. All substances absorbed in the higher parts of the intestines pass, on their way to the heart, through the portal

TABLE 2

Volume of one tenth per cent solution of Methylene blue decolorated by one gram of:

	cc.
Activated charcoal	11 to 25
Universal antidote	3.5
Bone charcoal	2.3
Carbo ligni	0.4

TABLE 3

SUBSTANCE	LETHAL DOSES FOR RABBITS WHEN ADMINISTERED (GM./KG.)		
	Per os	By subcutaneous injection	By intravenous injection
Pernocton	0.38	0.18	0.007
Digitalin	0.02	0.015	0.003
K-Strophanthin	0.02	0.0005	0.00025
Atropine sulfate	1.45	0.6	0.07
Coffeine	0.36	0.28	0.16
Strychnine	0.004	0.0005	0.0004
Chinine	1.5	0.2	0.07

TABLE 4

DURATION OF EXPERIMENT	CONTENTS OF CO_2
A. Diffusion of CO_2 through the skin into water	
minutes	*vol. per cent*
0	0
15	1.9
30	2.7
45	3.6
60	3.8
B. Diffusion of CO_2 from water of 8.7 vol. per cent contents of CO_2	
0	8.7
30	7.0
60	6.5
90	5.9
120	5.6

Table A gives the amount of CO_2 diffused from the skin into the distilled water.

Table B gives the decrease of CO_2 content by diffusion into the skin, when the water contains initially 8.7% CO_2.

vein and the liver. In the liver they are in part, or totally, either deposited or decomposed or diluted. When they reach the heart and the

systemic circulation they become diluted. From the rectum, however, which is richly vascularized and has an excellent absorptive power, the absorbed substances get into the hemorrhoidal plexus and through the hypogastric vein and vena cava directly to the heart, evading the *detour* through the capillary system of the liver. The greatest caution is, therefore, indicated in the rectal administration of potent drugs. Numerous deaths were caused about eighty years ago through therapeutic enemata of carbolic acid against Oxyuriosis. The once customary treatment of constipation in children by tobacco extract enemata often caused death. A prisoner desiring to conceal tobacco inserted it in the rectum; he died of nicotine poisoning. There are also murders by rectal administration of poisons on record.

Resorbtion from vagina and bladder. Of the other mucous membranes the *vaginal mucosa* has a good absorption power, not only for the administration of the male hormone, testosterone, but also for many poisons. Many fatal accidents have occurred from the use of bichloride of mercury solutions in vaginal douches, and during attempts at abortion. Administration of arsenic through the vagina has caused serious illness and death.

The mucous membrane of the healthy *bladder* does not absorb. When inflamed, however, it will readily absorb various substances.

Resorbtion from the skin. The absorptive power of the *skin* has been recently extensively investigated. It has been demonstrated that the intact, normal skin absorbed various gases, inorganic and organic solutions. There does not seem to be any doubt but that the skin is permeable to carbonic acid in both directions. This is a condition of pure diffusion. Resorption is proved by the dilatation of the capillaries of the skin in carbonic acid baths. Liberation of carbonic acid can be demonstrated when testing water in glasses which have been fixed on the skin (see table 4). Besides gases, the skin absorbs lipoid soluble substances readily, for instance *anilin oil*, *nitrobenzene*, methyl alcohol or *dichlordiacetylsulfide*, the well-known poison gas *Ypperite*, which is, in reality, a liquid. Inorganic poisons can also be absorbed. Repeated bathing of the feet in potassium bichromate for the treatment of excessive sweating, can result in fatal chrominephritis. Similarly, boric acid can be detected in the urine after the immersion of the feet for five minutes in a saturated solution of boric acid.

It is also known that metallic mercury is partly absorbed by the skin through the sweat and sebaceous glands. Mercury is changed into fatty acid salts and resorbed as such. A similar mechanism must have been in play in a case of thallium poisoning recently observed in this hospital. Broken skin, of course, absorbs much more readily. Wilkinson's ointment, for instance, often used in the treatment of scabies in children, can be dangerous and even fatal, as the highly noxious hydrogen sulfide which is formed, is easily absorbed through the broken skin.

CLINICAL PATHOLOGICAL CONFERENCES

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

Wednesday, March 1, 1939

Grawitz Tumor with Clinical, Laboratory and X-ray Findings Simulating a Colonic Neoplasm

(From the Medical Service of Dr. George Baehr)

History (Adm. 432705; P.M. 11008). The patient was a fifty-two year old white male, whose final illness began about three weeks before his admission to the hospital. At that time he began to complain of a dragging sensation in the right side of the abdomen and the right lumbar region. During this period there had been associated anorexia and constipation. Without catharsis there had been no bowel movements. There had been no nausea or vomiting. No bloody or tarry stools had been noted; aside from nocturia one to two times there were no genito-urinary symptoms.

Examination. The patient was a slow, obese, middle-aged male, complaining of right-sided abdominal pain. The chest was emphysematous. The lungs were clear. The heart was not enlarged; blood pressure was 120 systolic and 80 diastolic. The abdomen presented striking physical findings: it was markedly distended; the right flank was filled with an enormous nodular mass, the lower end of which reached one to two inches below the umbilicus. The relationship of the colon to this mass could not be determined. Neurological examination was negative. Rectal examination was not revealing.

Laboratory Data. Hemoglobin was 80 per cent; white blood cells, 13,900 with a normal differential. Sedimentation time, 30 minutes. Examination of the stool showed a 4 plus positive guaiac reaction on all specimens examined. The urine concentrated to 1.030, and only occasionally showed a trace of albumin; sugar, negative; microscopic examination, negative. Blood urea, 11; sugar, 90; cholesterol, 320; ester, 135; icteric index, 3; total protein, 6.8. Blood Wassermann reaction, negative. Echinococcus complement-fixation test, negative. Barium enema showed an irregular stenosis of the ascending colon such as is usually seen as the result of a neoplasm. Intravenous pyelogram showed a normal left kidney; on the right side the calyces and the kidney pelvis were somewhat dilated; the calyces retained their usual cupping; only the proximal inch of the right ureter was visualized. The roentgenologist felt that colonic neoplasm could be responsible for this picture by displacing the ureter mesially with secondary dilatation of the pelvis and calyces. Electrocardiogram showed no definite abnormalities.

Course. Although the clinicians agreed that the enormous size of the mass was most unusual for a neoplasm of the colon, nevertheless the presence of definite indications of colonic obstruction and the presence of blood in the stools were sufficient indications for operation. Consequently, the patient underwent an exploratory

operation. At operation the ascending colon was found to be fixed posteriorly by a neoplastic infiltration extending to the retroperitoneal tissue. Liver metastasis was seen. Because of its obvious inoperability, a palliative ileo-sigmoidostomy was done. Postoperatively the patient developed a diffuse bronchopneumonia; temperature, 102.4°F. On the fifth day after operation he suddenly developed profound pulmonary edema. He was energetically treated with tourniquets, Magendie, 50 per cent glucose intravenously, and a 500 c.c. phlebotomy, all without improvement. The patient died several hours after this episode.

Necropsy Findings. In the right hypochondrium, there was found a huge tumor arising from the lower pole of the right kidney. It extended forward and upward, invading the peri-renal tissues and fat, involving the pancreas and the ascending colon. The neoplasm had metastasized to the *liver, lungs,* the peri-portal *lymph nodes,* and to the peri-hilar *lymph nodes* in the *thorax.* On section, the tumor presented a mottled appearance with many yellowish areas such as are typically found in Grawitz tumors. In other areas, however, there was marked fibrosis. On microscopic section, the characteristics of a Grawitz tumor were evident. The *colon,* in its ascending portion, including the hepatic flexure, was invaded from behind by the tumor mass. The wall was rigid and the lumen was stenotic. However, there was no actual involvement of the colonic mucosa by the neoplasm. A gall stone was found in the common duct. The latter was not dilated.

Comment. Dr. Klemperer. Renal neoplasms so closely simulating a colonic neoplasm are infrequent. However, I have seen two similar cases.

Dr. Baehr. The picture fitted completely that of a colonic neoplasm. The presence of a positive guaiac reaction in the stool without any demonstrable mucosal involvement at autopsy could be explained as a result of interference with local circulation in the mucous membrane of the intestine. The presence of a stone in the common duct without icterus or definite symptomatology is not at all a rare finding. Even people with common duct stones who do manifest signs or symptoms may be perfectly well for long periods of time, with the stone remaining *in situ.* Roentgenologically, a mesial displacement of a ureter is found with neoplasm of the lower pole of the kidney, whereas lateral ureteral displacement is found in non-renal retroperitoneal tumors.

Wednesday, March 8, 1939

Staphylococcus Aureus Bacteremia Secondary to Chronic Furuncle of Thigh. Acute Bacterial Endocarditis of Tricuspid Valve. Uremia due to Acute, Diffuse Glomerulonephritis; Increase in Cerebrospinal Fluid without Meningitis

(*From the Medical Service of Dr. B. S. Oppenheimer*)

History (Adm. 433524; P. M. 11024). This seventeen year old boy was admitted to the hospital on December 14, 1939 because of headache and fever of five days' duration. His past history was negative except for occasional colds and nosebleeds. Three months before admission he developed a furuncle of the right thigh which never healed completely. Five days before admission, while playing basketball, he was hit on the

head with the ball. The injury was a slight one, resulting apparently only in a contusion above the left eye. The next day he complained of a headache, followed by general malaise and a rise in temperature to 104°F. The day before admission he vomited several times. That night he had a severe nosebleed which necessitated packing of the nose before it could be controlled. The day of entry he again vomited, the vomitus containing blood, presumably secondary to the epistaxis.

Examination. The boy was disoriented as to time and place, but was cooperative. There was a contusion of the left upper lid. Pupils reacted well. Bloody crusts were present in both nares and ruptured vessels were seen on both sides of the nasal septum. Small, non-tender nodes were palpable in the posterior cervical, axillary, and inguinal regions. The lower pole of the spleen was palpable on inspiration. Over the right thigh was an indurated erythematous area. The fourth cervical spine was tender and moved with soft crepitus. Temperature on admission was 101.5°F. The heart was normal; there were no murmurs. Blood pressure was 112 systolic and 66 diastolic.

Laboratory Data. Hemoglobin, 70 per cent; red blood cells, 4,000,000; white blood cells, 11,400 (82 per cent polymorphonuclear neutrophiles; 44 per cent of which were non-segmented). Blood urea, 19; sugar, 135. Urine: specific gravity, 1.024 with a trace of albumin, no sugar; microscopic examination showed an occasional white blood cell, red blood cell, and epithelial cell, but no casts. Blood Wassermann test was negative. Culture of aspirated material of the furuncle revealed a Streptococcus hemolyticus Beta.

Course. The temperature, which was 101.4°F. on admission, rose sharply to 105.4°F. The diagnosis was sepsis. The next morning he developed signs of meningeal irritation, nuchal rigidity, bilateral Kernig and Babinski signs. A lumbar puncture revealed clear cerebrospinal fluid under an initial pressure of 180 mm. There were 50 cells per cu. mm., most of them being polymorphonuclear neutrophiles. Culture and smear of the fluid were negative. Serology was negative. Chemistry of the spinal fluid revealed normal sugar, total protein, and chloride concentrations. The sinuses were investigated as a possible source for the meningeal signs. Only a few flakes were found in the left sphenoid sinus. On culture, a Staphylococcus aureus was obtained. At this time, the blood culture was reported as showing innumerable colonies of Staphylococcus aureus; the urine culture likewise showed Staphyloeoccus aureus. The patient was, therefore, vigorously treated with daily transfusions, and daily administration of Staphylococcus antitoxin, as well as sulfapyridine. His condition, however, failed to improve. The temperature continued to swing up to 105°F. The meningeal signs persisted. A second lumbar puncture showed an increase of the pressure to 240 mm. with no evidence of block. Cell count was 18 per cu. mm., 75 per cent being mononuclear cells. Smear and culture were again negative for any organisms. A few days after admission he developed tenderness and swelling at the anterior aspect of the left shoulder, which was felt to be an early metastatic bursal infection. He then developed dulness and râles at both bases. Bedside X-ray examination of the chest now showed small mottled areas of consolidation which the roentgenologists felt were compatible with the presence of multiple metastatic inflammatory lesions. An apical systolic murmur, not present on admission, soon became audible. Cyanosis and dyspnea developed, and became progressively more marked; there was an associated tachycardia. Two days before death, severe oliguria appeared. At this time the urine showed a four plus albumin and one to two red cells per field microscopically. The blood pressure rose to 175 systolic and 80 diastolic. A blood urea examination revealed a sharp elevation to

122 mg. per cent. Therefore, the patient was believed to have developed a renal lesion resulting in uremia. He gradually became comatose, and died on the seventh day of hospitalization in a convulsive seizure.

Necropsy Findings. Examination of the *heart* revealed the presence of an acute, bacterial endocarditis of the tricuspid valve. The valve contained several pearly-gray, well-rounded excrescences, measuring one to two millimeters in diameter. The endocardium of the septum below the septal leaflet of the tricuspid valve was covered by a large vegetation composed of heaped-up, friable, yellowish-gray material. Sections and bacterial stains revealed Gram-positive cocci in clusters. The *lungs* were studded with multiple abscesses, some of which were on the surface. The pleura was of dull luster showing the early phase of fibrinous pleuritis. The *spleen* was large, and presented the soft swelling typical of sepsis. The *kidneys* were enlarged and edematous. The capsules stripped with ease, exposing mottled, pinkish-tan surfaces. In addition, there were present on the surfaces a few reddish flecks with gray centers, about 3 mm. in diameter. On section, these revealed soft, creamy white pus. Throughout the renal parenchyma there were present multiple abscesses, both cortical and medullary. Histologically, in addition to the presence of embolic suppurative lesions, there was definite evidence of an acute diffuse glomerulonephritis.

Comment. Dr. Baehr: An interstitial suppurative nephritis occurring in the course of a sepsis might well account for the presence of uremia. However, the presence of hypertension suggested the existence of acute glomerulonephritis as an additional complication.

Dr. Klemperer: The presence of a furuncle, the Staphylococcus aureus sepsis, the finding of Streptococcus hemolyticus in the furuncle, and the nephritis can all be correlated by emphasizing the presence of mixed infection in the furuncle, so that the sepsis could be attributed to the Staphylococcus aureus, and the acute glomerulonephritis correlated with the presence of the Streptococcus hemolyticus.

Thrombocytopenic Purpura (Symptomatic). Carcinoma of Prostate with Symptoms due to Extensive Bone Marrow Metastases

(From the Medical Service of Dr. B. S. Oppenheimer)

History (Adm. 433687; P. M. 11030). The patient was a fifty-six year old man who, for many years, had been employed as a tailor. His past history was essentially negative. His illness began ten weeks before admission with the occurrence of pain across the lower part of the back on movement. A plaster was applied locally several times without much relief. Six weeks before admission he began to void dark brown urine; at the same time ecchymotic areas appeared on the arms and legs. Increased diurnal frequency and nocturia occurred and because of this he was cystoscoped. After that time, although there was some relief of the back pain, there was frank hematuria associated with some incontinence. Four weeks before admission he was admitted to another hospital. Two cystoscopies were performed and were said to have been negative. He was then given a blood transfusion. Following the trans-

fusion, the purpuric areas on the extremities began to clear, and the urine gradually became less bloody with bladder irrigations. However, small purpuric spots continued to appear. He was discharged from that hospital ten days before admission to the Mount Sinai Hospital. One week before admission several large ecchymoses appeared on the lower extremities. At the same time he noted that his stool was black on two occasions. Two days before admission he spontaneously developed an ecchymosis around the left eye; bleeding from the gums had occurred and there had been a recurrence of the low back pain. For the two weeks before admission there had been no hematuria or incontinence. During his illness he had lost eleven pounds in weight. There was no known exposure to, or ingestion of, any of the known hematotoxic agents.

Examination. The patient was well-developed and well-nourished. There was a left periorbital ecchymosis. Aside from narrowed arteries, the fundi were negative. The gums were spongy and bled easily. Numerous moist râles were present at both lung bases. The heart was normal. Blood pressure was 130 systolic and 80 diastolic. The spleen was palpable one finger-breadth below the costal margin. This was felt with difficulty because of tenderness and muscle spasm in the left upper quadrant. The prostate gland was uniformly enlarged. Above the prostate, there were felt a number of hard, irregular nodules. There were numerous large ecchymotic areas, most marked over the lower extremities, but having a generalized distribution. Marked limitation of spine flexion with spasm of paraspinal muscles was present. The left knee and ankle jerks were markedly diminished. Temperature was normal.

Laboratory Data. Hemoglobin, 70 per cent. Red blood cell count was 3,790,000; white blood cell count, 10,700 (56 per cent polymorphonuclear leucocytes; 3 per cent eosinophiles; 1 per cent basophiles; 26 per cent lymphocytes and 7 per cent monocytes). No abnormal cells were seen. Platelet count was 90,000. Reticulocyte count was 0.5 per cent. Bleeding time was nine minutes while the coagulation time was over one hour. Aspiration of the sternal bone marrow revealed clumps of malignant tumor cells. The urine concentrated to 1.020; there was a faint trace of albumin and no sugar; microscopically, there was an occasional white blood cell and a few epithelial cells. The blood Wassermann test was negative. The blood chemistry showed: urea nitrogen, 20; sugar, 95; cholesterol, 350; calcium, 10.9; phosphorus, 4.2 mg. per cent. The icteric index was 3. The total protein was 6.6 per cent with an albumin of 5.2 and globulin of 1.4. Sedimentation time was one hour, forty minutes. Electrocardiogram showed a left ventricular hypertrophy. X-ray examination of the chest showed no abnormality in the heart and lungs. An irregularity of the axillary portion of the sixth rib on the right side was noted. This was characterized by the formation of a local area of excess bone production. Sigmoidoscopy revealed normal mucous membrane except for a marked tendency to bleed. Immediately above the prostate there appeared to be an infiltration. Stool on admission was guaiac negative.

Course. The diagnosis was symptomatic thrombocytopenic purpura, due either to leukemia or metastatic malignancy. In view of the findings on sternal aspiration and chest X-ray examination, it seemed apparent that this man had a neoplasm with multiple bone metastases. The primary focus was not definitely ascertained, although the prostate was suspected because of its firmness. Although the stool was guaiac negative on admission, there soon appeared frank rectal bleeding with the passage of bright red blood. In spite of five citrate transfusions, his hemoglobin

fell to 34 per cent. The platelet count also fell to 35,000. He ran a low-grade fever which, terminally, rose to 103°F. His course was rapidly down-hill and he died eleven days after admission.

Necropsy Findings. The *prostate gland* was enlarged to twice the normal size and projected into the bladder as a small, but distinct, median bar. On section, the normal architecture of all lobes was destroyed, being replaced by a firm, cellular, gray-white nodular tissue in which were many hemorrhagic areas. The tumor was well-encapsulated except posteriorly where it infiltrated into the adjacent peri-rectal and peri-vesical fat tissue in the pouch of Douglas. The microscopic examination confirmed the gross diagnosis of carcinoma. Aside from a very small metastatic nodule in the *lungs*, all other gross metastases were completely confined to the bones. In all the *bones* examined (vertebrae, sternum, and right sixth rib) there were extensive nodules, not associated with any osteosclerosis or new bone formation. Microscopically, in addition to a very marked infiltration of the bones, there was definite involvement of the subpleural lymphatic and peri-arterial and peribronchial lymph spaces. The *spleen* was enlarged, weighing 550 grams; this was a result of extramedullary blood formation, chiefly of the erythropoietic series, but also including megakaryocytes. This process was most evident within, though not completely confined to, the sinuses of the spleen. The *liver* also was the site of erythropoietic activity, but to a much lesser extent. Throughout all the organs, there were evidences of well-marked hemorrhagic diatheses; thus, there were petechial hemorrhages and ecchymoses in the skin, serous membranes, diaphragm, trachea, bronchi, renal pelvis, and massive hemorrhage into the gastrointestinal tract.

Comment. Dr. Baehr: Essentially, this man died from symptomatic thrombocytopenia and its attendant hemorrhagic manifestations. The thrombocytopenia was secondary to the diffuse bone metastases.

Dr. Klemperer: The vast majority of prostatic carcinomas that metastasize to bone produce osteosclerosis. This case was unusual in that there was bone destruction, rather than proliferation.

Dr. Saul Jarcho: It is very unusual for a carcinoma of the prostate to produce purpura from metastases. In cases with purpura, there is no grossly visible bone involvement, either to the eye or the x-ray. In these instances, microscopic examination reveals a diffuse infiltration. There is a possibility of mistaking this purpura, when accompanied by splenomegaly and hepatomegaly (secondary to extramedullary erythropoiesis) for leukemia.

Reported by *Max Ellenberg, M.D.*

CLINICAL NEUROPATHOLOGICAL CONFERENCE

Monday, February 13, 1939

JOSEPH H. GLOBUS, M.D., *Presiding*

*Case 8.** Alzheimer's Disease (Presenile Dementia)

(From the Neurological Service of Dr. I. S. Wechsler)

History (Adm. 406257; P. M. 10313). A woman, 56 years old, was admitted to the hospital March 25, 1937. Her past personal history was marked by an intestinal resection which she had undergone in 1915, and by a period of three years (1928 to 1931) in which varicose veins in both lower extremities with abscess and ulcer formation necessitated several admissions to the hospital. Her fatal illness began insidiously four years before the final admission. Her family noticed that the patient was becoming forgetful, particularly when marketing and handling money. During the next two years she displayed progressive slowing of activity, a gradual loss of initiative, more frequent lapses of memory, and a diminishing interest in her surroundings. Finally she could no longer take care of herself and had to be guided in all her efforts, even had to be fed. She began to lose weight and lost 50 pounds in the course of one year. The decline in her condition became more and more rapid in the last six weeks before admission, when she became subject to recurrent attacks of "weakness." These attacks increased in frequency and duration to such an extent that she became bedridden two weeks before admission. At the same time her memory failed almost completely. Incontinence set in and four days prior to admission she became stuporous.

Examination. The patient was obese and looked older than her given age. She was in semi-stupor and tossed restlessly in bed, picking at the bed covers and babbling incoherently. Periodically her limbs would flex and extend. There was a marked resistance to flexion of the neck. The retinal vessels showed a moderate sclerosis. The right pupil was smaller than the left and did not react to light. There were myoclonic twitchings of muscles of the face and legs, as well as a general tremulousness of all extremities. The deep tendon reflexes were all hyperactive but less so in the left lower extremity. The Hoffman signs were elicited bilaterally. There was an equivocal Chaddock sign on the right side. The blood pressure was 115 systolic and 70 diastolic.

Laboratory Data. Blood sugar, 130 mg. per cent; blood cholesterol, 205 mg. per cent; phosphorus, 4.0 mg. per cent; calcium, 10.6 mg. per cent. Blood examinations were otherwise negative. The cerebrospinal fluid was normal in all phases. The Wassermann tests on the blood and cerebrospinal fluid were negative.

*The first seven cases were reported in previous issues (Vol. 6, No. 4-6).

Course. The diagnosis rested between Alzheimer's disease and metastatic brain tumor. The patient continued in a state of semi-stupor. She developed pneumonia and died six days after admission.

Necropsy Findings. Brain. Gross. The leptomeninges were milky and opaque. The cerebral hemispheres were small. Their convolutions were narrow and the sulci gaped, particularly in the frontal and parietal regions.

On sectioning, the cerebral hemispheres disclosed a moderate amount of cortical atrophy, slight and symmetrical enlargement of the ventricles, and a moderate increase in the consistency of the brain.

Microscopic. Sections from various regions of the brain were stained by the hematoxylin-eosin, Nissl (toluidin blue), and Bielschowsky techniques and by the Globus modification of the Cajal gold sublimate and Hortega (variants I and III) stains. Numerous senile plaques were found widely distributed in the cerebral cortex and basal ganglions. They stained intensely with all the silver stains (fig.

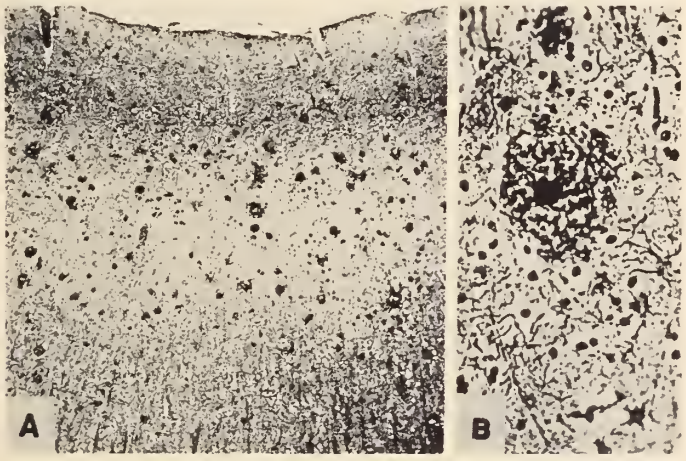

FIG. 23 (Case 8). *A.* Section of the cerebral cortex showing numerous senile plaques (Hortega silver carbonate, Globus modification, microphotograph, 90 ×). *B.* A senile plaque under higher magnification (Hortega silver carbonate, Globus modification, microphotograph, 200 ×).

23A). Their size and appearance varied considerably. Most numerous were circular plaques composed of short, irregular argentophilic fragments which were usually arranged in haphazard fashion, although in some plaques there was a suggestion of a spoke-like radial arrangement (fig. 23B). There were a few forms in which a mass of argentophilic material, resembling a ganglion cell, was located in the center of the plaque. A rare form was found in which the plaque seemed to have formed around a small blood vessel.

The cerebral cortex showed a disorganization of its lamellar arrangement and a marked decrease in the number of nerve cells (fig. 24A). The nerve cells themselves contained an increased amount of argentophilic deposits. Many were sclerotic and stained uniformly black with silver (fig. 24B). In some nerve cells, the neurofibrillae had lost their discreteness and uniform distribution and were masses at the periphery of the cell or coiled in thick bands within it (fig. 25). With the Nissl stain, some nerve cells showed a hyaline appearance and complete loss of Nissl

substance. In the cerebellum, a silver-pyridine block preparation showed a Purkinje cell with an oval argentophilic expansion along its axon.

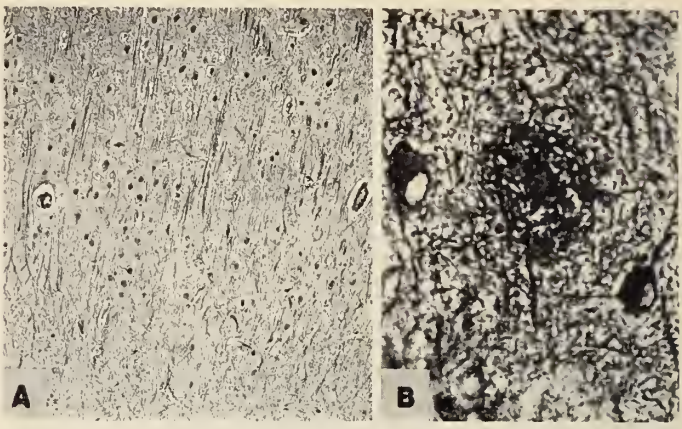

FIG. 24 (Case 8). *A*. Cerebral cortex showing a marked decrease in the number of nerve cells and the resultant disorganization of the lamellar architecture (Bielschowsky, microphotograph, 90 ×).

B. A senile plaque surrounded by nerve cells undergoing fibrillary changes (Hortega silver carbonate, Globus modification, microphotograph, 500 ×).

FIG. 25 (Case 8). Typical (Alzheimer) neurofibrillary alterations in nerve cells (Hortega silver carbonate, Globus modification) (drawing; ocular, 15 ×; objective 40; numerical aperture 0.65).

Glial elements were markedly increased throughout the brain and many corpora amylacea were seen (fig. 26).

Comment. It was in 1907 that Alzheimer described the first case of the disease for which Krepelin adopted the name Alzheimer's disease. The case was that of a woman, aged 51, who presented a history of progressive loss of memory, mental disorganization and confabulation, which culminated in a pronounced dementia. Alzheimer noted in this case the presence of striking pathological findings and named this condition fibrillary disease. His report initiated further studies of this form of presenile dementia and about 100 cases have been reported to date.

The pathological changes in this disease have as their areas of predilection the frontal lobe and the hippocampus major. They are characterized by degeneration and disappearance of nerve cells, particularly in the

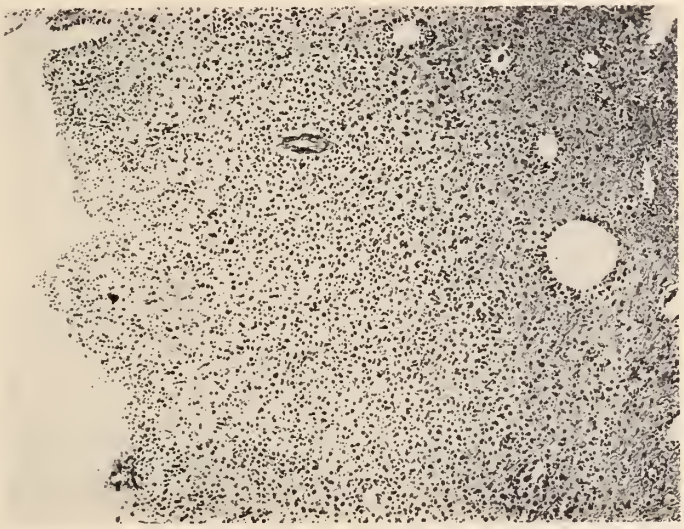

FIG. 26 (Case 8). A section of the cornu Ammonis crowded with corpora amylacea (Hortega silver carbonate, Globus modification, microphotograph, 93 ×).

cortex, and disorganization of neurofibrillae which form whorls and tangled masses, nests and basket-like arrangements. This is well-demonstrated with the Bielschowsky stain. Glial elements, particularly fibroblastic astrocytes, are increased in number. But, above all, there are the so-called senile plaques. The origin of the latter is still a matter of dispute. Some claim that they arise from neuroglia and others trace them to disintegrated nerve cells. It is probable, as many believe, that they originate from both diseased nerve cells and neuroglia. It is significant that some investigators have found all of the above changes in chronic encephalitis and in senile dementia and assume the existence of the same cause. On purely pathological grounds, therefore, the diagnosis may at times be difficult.

There appears to be an hereditary factor, as an instance has been reported in which Alzheimer's disease occurred in three successive generations, while in another instance, a father and two daughters were afflicted by this disease.

The cases reported in the literature indicate a far greater incidence of this disease among women.

The age in which the disease is prevalent, as its designation presenile dementia would indicate, is between the fifth and sixth decade, though cases have been reported at much earlier ages. In one case, reported as Alzheimer's disease, symptoms appeared at the age of 7 and death occurred at 24 years. In another case the first symptoms appeared at 24 years and death at 39 years.

The duration of the disease varies from about eight months to about twenty years.

The diagnosis of Alzheimer's disease is most commonly based on its occurrence in the presenile age, the gradual progressive loss of memory, the manifestation of further intellectual deterioration, confabulation to fill memory gaps, confusion, restlessness, and disorientation for place, time, and person. Convulsions are often present in the later stages of the disease.

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

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.

Pruritus Ani: a Simple and Efficient Treatment. Howard Lilienthal. J. A. M. A. 110: 509, February 1938.

Most cases of pruritus ani can be relieved by simpler means than operative surgery. The following method has proved almost uniformly successful over many years.

Minute cutaneous fissures are contaminated by fecal matter rubbed into them during cleansing after stool, and the consequent irritation produces itching. The treatment is as follows: First cleanse the parts with any noninflammable grease solvent, such as carbon tetrachloride to which a small proportion of benzine may be added. Then expose the region to the air until the skin is dry. This seldom has to be repeated. Fill completely and carefully all the tiny fissures with some bland substance such as zinc oxide ointment.

The patient is instructed to apply a thick coating of zinc ointment or 25 per cent Liquor Burowii in aquaphor *before* each evacuation. After stool, cleansing with soft paper will suffice; ordinary soap and water may be used once a week. After a few weeks of treatment without recurrence, healing may be assumed. Prevention of soiling sensitive skin will avoid recurrence.

The Relative Refractory Period of Olfaction and of Vision. H. Spotnitz, and Charles A. Elsberg. Bull. Neurol. Inst. N. Y., 7: 78, March 1938.

The temporary lack of ability of an individual to perceive and to recognize the nature of a weak stimulus following strong excitation may be called the relative refractory period. The duration of this period is, in all probability, primarily determined by the centrally situated neurones. Its duration varies according to the well known principles of summation, facilitation, and occlusion. The prolongation of the relative refractory period of olfaction and of vision in cases of tumors of the brain is an indication of the effects of the neoplasm on the *functions* of the affected areas.

Ten Years Research of Dental Infections and Their Relations to Systemic Disease. H. A. Goldberg. Am. J. Orthodontics, 24: 272, March 1938.

In ruling out the teeth as a possible focus in systemic disease, the dental medical history is of utmost importance. If the infected teeth and gums are the primary factor, the dental history will antedate the medical history. The macroscopic, clinical, and radiographic examinations should be made concomitantly while the patient is present, as not infrequently the radiographic findings may differ with the clinical findings.

All teeth harboring infection should be treated. They should not necessarily be extracted, for if such teeth are properly sterilized they often will remain sterile. Dr. Wycoff, the former Dean of New York University Medical College, found from his clinical experience that it took approximately twenty years before infected teeth manifested themselves in a cardiac disease, and that not infrequently, with the extraction of these teeth, the cardiac disease definitely improved.

Sixty-two patients under investigation were given autogenous vaccines. Fifty-four of these showed good results and only eight showed no results.

Tobacco Sensitization in Rats. J. Harkavy. Allergy. 9: 275, March 1938.

This paper is a preliminary report on the experimental production of tobacco sensitization in rats, supplementing the author's clinical studies of tobacco allergy in patients suffering from vascular disorders such as thrombo-angiitis obliterans and certain forms of coronary artery disease. Sensitization was induced by the daily intraperitoneal injection of one c.c. of a pooled tobacco extract within a period of six to ten weeks, and demonstrated by the Schultz-Dale technique, utilizing the intestinal strip of the male and the uterus of the female rats.

Twenty-two rats were studied; fifteen of these were injected with tobacco, and seven were used as controls. Of the former, twelve were males and three, females; of the latter six were males and one, female.

Five males injected with the pooled tobacco extracts developed gangrene of the toes, and showed sensitization to tobacco.

Of six male rats injected with tobacco who did not develop gangrenous lesions, only three showed tobacco sensitization.

In four rats who, in addition to tobacco, were injected with horse dander, egg white or ragweed, no evidence of sensitization to any of these substances could be demonstrated.

None of the three female rats injected with tobacco developed gangrene of the toes, and no evidence of tobacco sensitization could be obtained.

Lymphepithelioma of the Mediastinum—Metastatic. L. Kleinfeld and G. Y. Smith. Laryngoscope, 48: 204, March 1938.

A case is presented of a tracheal neoplasm which was reported as lymphepithelioma. The patient later developed, according to x-ray evidence, a fistula between the trachea and the esophagus. Repeated clinical examination of the nasopharynx was negative but specimens taken at various areas in the nasopharynx were reported to be lymphepithelioma. This undoubtedly was the original source of the metastatic lesion in the chest.

Tuberculosis of the Petrous Pyramid. L. Kleinfeld and G. Y. Smith. Ann. Otol. Rhin. & Laryngol. 47: 261, March 1938.

A child with a combined infection of tuberculosis and schistosomiasis developed an aural discharge which finally required a radical mastoidectomy. The appearance of the ear and mastoid was so strongly suspicious of tuberculosis that numerous smears, cultures, and specimens were removed, although the diagnosis was not verified. The child had a facial paralysis on the affected side, which cleared up temporarily after the first operation but later recurred. In spite of a second thorough radical mastoidectomy, a persistent discharge came through the wound until the patient's death. Post mortem examination showed miliary tuberculosis and tuberculomata on the surface of the petrous pyramids, one of which communicated with a necrotic area which, in turn, involved the facial canal.

Effect of Subcutaneous Injections of Concentrated Spleen Extract on Mouse Sarcoma 180. R. Lewisohn. Surg. Gynec. & Obst. 66: 563, March 1938.

Of 281 animals treated with subcutaneous injections of 0.5 cubic centimeter of concentrated spleen extract (100 gm. of fresh spleen in 1 cu. cm.) the tumor (sarcoma 180) disappeared completely in 170 animals (60 per cent). Corresponding controls showed a spontaneous regression in 8 per cent of 290 animals. Injections extending usually over 2 to 6 weeks, depending upon the original size of the tumors, are required to cause disappearance of the tumors. Weight gain is an early sign indicating subsequent disappearance of the tumor. Small doses of the extract (0.1 cu. cm.) have a stimulating effect upon the tumor. A marked increase in the size of the spleen is noted in the animals treated with spleen extract. Animals treated with other organ extracts and controls do not show this enlargement. Extracts from the liver, heart, pancreas, and testis fail to cause hemorrhages into the tumor or to influence its growth. The spleen extract does not show the Shwartzman phenomenon.

Anaerobic Infections Following Operations on the Urinary Tract. W. E. Mencher and H. E. Leiter. Surg. Gynec. & Obst. 66: 677, March 1938.

Anaerobic infections following operations are serious complications, attended by a high mortality. Fourteen cases are analysed in which operations were performed on the urinary tract. In eleven cases the infection was caused by B. welchii and in three cases by B. tetani. The mortality for the B. welchii infections in this series was 18 per cent. The mortality in the three cases of B. tetani was 100 per cent.

The various possible sources of infection are discussed. Early recognition of anaerobic infections in the wound and early and adequate treatment are essential factors in keeping the mortality rate low. In the cases of tetanus the appearance of symptoms is usually significant of late manifestations of the disease. The appearance of the wound in these cases is of no aid in the diagnosis. Any unexplainable neurological symptoms must take into consideration the possibility of tetanus.

Protamine and Insulin Therapy. H. Pollack and H. Lande. N. Y. State J. Med. 38: 339 March 1, 1938.

This report represents the experiences of the Metabolic Group at The Mount Sinai Hospital with protamine zinc insulin during its first year of use. The report is optimistic as to the eventual use of this new therapeutic agent. Several practical details in the handling of this agent are given. Indications are given that changes in diet prescription will be necessary. Detailed protocols are given for several patients.

Organs as a Source of Factors Capable of Eliciting the Shwartzman Phenomenon. W. Antopol and D. Glick. Proc. Soc. Exper. Biol. & Med., 38: 346, April 1938.

Fractions prepared from pancreas, testis, liver, kidney, brain, placenta, muscle, breast, and uterus were shown to possess provocative Shwartzman phenomenon factors, although the results were irregular in some cases. Similar fractions from spleen gave negative results. Only the fractions from the first three of these tissues were also tested for preparatory potency, and were found to elicit positive reactions.

Decreased Choline-Esterase Activity of Serum in Jaundice and in Biliary Disease. W. Antopol, A. Schifrin and L. Tuchman. Proc. Soc. Exper. Biol. & Med. 38: 363, April 1938.

The choline-esterase activity of the serum in patients with jaundice or biliary tract disease was found to be depressed. A possible relation of the depressed choline-esterase activity to the sweating, bradycardia, and fall in respiration, vagotonic symptoms which not infrequently occur in cases of hepatic disease with and without jaundice, is suggested.

Prophylaxis Against Measles with the Globulin Fraction of Immune Human Adult Serum. S. Karelitz. Am. J. Dis. Child. 55: 768, April 1938.

Earlier studies have indicated that the whole globulin extracted from the blood of adults who had had measles in childhood, was effective in prophylaxis against measles. This offered a method of concentration of measles antibodies, making it possible to use volumes of one-twelfth to one-twentieth of the original blood with results equally good to those expected with whole blood. Method for preparation of the globulin and charts giving accounts of the individual case reports are published. The use of immune adult serum globulin in measles prophylaxis is recommended because it is easily prepared from readily available adult blood; the final preparation can be stored and transported without loss of antibody, the procedure of injection is simplified, and danger of transmission of infection by use of whole blood is removed.

Hemorrhage from the Throat. L. Kleinfeld. Laryngoscope, 48: 253, April 1938.

The three cases discussed in this article, all of whom died, with post mortem examination being performed on two, emphasize the following points: hemorrhage from the throat, when recurrent, large in amount, or associated with hemorrhage from the ear, indicates the near approach of a fulminating fatal hemorrhage. The only treatment of any value is ligation of the carotid artery, in spite of the fact that this procedure is, in itself, associated with a certain mortality.

Netting Restraint Over Hospital Crib. J. L. Kohn. J. Pediat., 12: 524, April 1938.

Various devices are being used to prevent active young children from falling out of hospital cribs. The most common in use is a canvas vest with attached tapes which tie at the sides of the bars. The above restraint limits the child's movements and is harmful physically and psychologically.

An ordinary tennis netting (1 inch by 1 inch) mounted on a light metal frame was devised. The frame is fastened to the side bars of crib with web straps. A hinge is provided which makes it possible to leave the frame intact when tending the child.

The advantages are: (1) there is little restraint except on standing; (2) the child cannot harm himself; (3) the frame is ready for immediate use; (4) the netting can be easily sterilized and the frame can be thoroughly washed.

Aqueous Preparations to Supplant Oil in Roentgenography. H. Lilienthal. Am. J. Roent. & Rad. Ther. 39: 564, April 1938.

Because of the danger of oily substances of any kind in the lower respiratory tract, because of the occasional lighting up of pulmonary tuberculosis from iodized oil, and because iodized oil not infrequently remains as a permanent opaque area in the chest, the writer advises that it be supplanted by a 30 per cent suspension of iodoform in syrupy glucose (U. S. P.), diluted with sufficient water to suspend the iodoform and permit its use in the bronchi. The iodoform is of therapeutic value in tuberculosis instead of acting as an irritant, and it is quickly absorbed. The syrupy solution also rapidly disappears. As in iodine, so in iodoform: the patient should be tested for allergy.

Recurrent or Residual Progressive Ileitis. G. D. Oppenheimer. J. A. M. A. 110: 1103, April 2, 1938.

A classification of the non-specific inflammatory lesions of the bowel was presented by Ginzburg and Oppenheimer in 1932. One of the cases illustrative of the group called "regional ileitis" is presented in detail because of the interesting subsequent course. This patient was found to have a recurrence of the disease following apparently adequate resection. Similar cases were found in the literature indicating that permanent cure in these cases will not always follow resection.

Studies on Biologic Effect of Colored Light. H. Vollmer. Arch. Phys. Ther. 19: 197, April 1938.

The literature is reviewed and personal observations on the effect of colored light are given. (*1*) The germination of lentils is delayed and their growth stimulated by red light. These results are considered to be phenomena of etiolation—not a specific effect of red light. (*2*) Guppies show a preference for blue, ants for red light; flies do not seek either blue or red light. These findings are explained by the natural preference of certain animals for daylight, semi-darkness, and darkness respectively. (*3*) Red light does not influence the growth of rats, nor does it have any effect on the calcium and phosphorus content in the serum, the bone formation, or the cell structure of the hypophyses, ovaries or testes. (*4*) The "photodermatic tonus reflex," described by Ehrenwald as a tonus reaction to blue and red irradiation of the skin, was not confirmed. (*5*) Red room treatment definitely prevents suppuration and scar formation in variola. This is a "negative light therapy"—i.e. the effect is due to the exclusion of chemically active rays, but not to the specific effect of red light. (*6*) A specific influence of red light in erysipelas, erythemas, exanthemata, or lupus erythematodes disseminatus was not proved. (*7*) The ultraviolet erythema can not be influenced by subsequent irradiation with red light. (*8*) Red light irradiation does not influence the capillaries of the normal skin. (*9*) The limits of "chromotherapy" and its psychic component are discussed.

A Sheet Bandage for the Treatment of Eczematous Children. H. Vollmer. J. Pediat. 12: 522, April 1938.

A method is described for wrapping an eczematous child in a sheet so that changes in posture and movements of the arms remain possible, and yet scratching of the body or face is prevented. The child is placed in the middle of a sheet—the neck lying upon its upper edge. The sheet is then folded from both sides over the shoulders and arms, drawn under the armpit, then around the back, and knotted above the chest. The lower edge of the sheet is finally drawn up between the legs and fastened with safety pins on both sides in the region of the shoulder.

Love at First Sight as Manifest in "The Tempest." Ira S. Wile. Am. J. Orthopsychiatry. Vol. VIII. No. 2. April 1938.

The truth of literature lies in its basic psychological consistency. An analysis of the reactions of Miranda and Ferdinand over a period of four hours indicates the reasonableness of their love at first sight in the presence of a state of mental tension that is prepared thoroughly for the recognition of love. The transformation of her filial obedience to parental rejection with dependence upon Ferdinand and his assumption of emancipation from paternal direction lead to their mutual acceptance of identical personal values. The text reveals the obvious fusion of normal adolescent emotional life into a psychologically consistent belief in the permanence of their plighted affections on the foundation of an emotional preparedness for reciprocal affections.

Calcium Studies in the Newborn. B. S. Denzer, M. Reiner and P. Vogel. Proc. Soc. Exper. Biol. & Med. 38: 492, May 1938.

The relationship between the calcium of the cord blood and that of the peripheral blood during the first ten days of life was studied. If a low cord blood calcium regularly were associated with a low calcium during the first ten days of life, then hypocalcemic tetany of the newborn could be predicted and prevented. There is a tendency for the serum calcium to assume values lower than the cord blood during the first four days of life and then to rise toward the prenatal level during the next five days. Studies of other factors—inorganic phosphorus, total protein, blood cell

concentration, feeding, etc.—are being continued to determine what circumstances may influence the calcium level variations.

Anaphylactic Gangrene Following Administration of Horse Serum. Arthus or Shwartzman Phenomenon? J. L. Kohn, E. J. McCabe, and J. Brem. Am. J. Dis. Child. 55: 1018, May 1938.

The case presented is one in which a patient, ill with a septic sore throat and sensitive to horse serum, developed extensive gangrene after repeated injections of horse serum at short intervals. This reaction has been commonly called "Arthus reaction" and can be experimentally obtained in rabbits by injection of horse serum at weekly intervals. In humans, however, we believe it occurs only in the presence of an acute bacterial infection such as a septic sore throat, scarlet-fever, and diphtheria. The role of the Shwartzman phenomenon in such a reaction is discussed.

Explanation for the Cyanosis of Sulphanilamide Therapy. R. Ottenberg and C. L. Fox, Jr. Proc. Soc. Exper. Biol. & Med. 38: 479, May 1938.

When sulphanilamide in suitable dilution is radiated with ultraviolet light it develops a strong violet color. It is believed that this same violet substance is produced in the body (without the intervention of light) and stains the red blood cells, thus causing the appearance of cyanosis.

Hypoglycemic Response of Patients using Protamine Zinc Insulin to Indueed Hyperglycemia. H. Pollack and H. Dolger. Proc. Soc. Exper. Biol. & Med. 38: 577, May 1938.

Evidence is presented to show that the use of protamine zinc insulin in the treatment of diabetes mellitus restores carbohydrate tolerance to a more normal type than that obtained with old insulin. The glucose tolerance curve in the patient with mild diabetes approximates the normal tolerance curve. In severe diabetics, the hyperglycemia invariably induces a subsequent hypoglycemia.

Skin Absorption of Dihydroxyestrin in Humans. U. J. Salmon. Proc. Soc. Exper. Biol. & Med., 38: 481, May 1938.

The absorption of the estrogenic hormone through the human skin was investigated in 14 women whose vaginal smears indicated marked estrogen deficiency. The estrogen used was dihydroxyestrin in a lanolin base varying in concentration from 500 to 25,000 R. U. per ounce. Absorption was estimated on the basis of the application to the human female of the Allen-Doisy test. The vaginal smears were prepared by the Fuchsin method. (Salmon and Frank, Proc. Soc. Exp. Biol. & Med., 33: 612, 1936.) The patients applied the estrogen ointment to the face, neck, and chest nightly, in amounts varying from 500 to 10,000 R. U. per week. Of the 14 cases treated, a full estrogen effect (reaction IV) was produced in 4; an incomplete effect (reaction III) in 2; a slight effect (reaction II) in 6, and no reaction in 2 cases. The full estrogen effect was produced with total doses varying from 160,000 to 300,000 R. U. Cases using 500 R. U. per week showed no estrogen effect at the end of 12 weeks. The threshold of absorption as manifested by the vaginal smear reaction appears to be upwards of 10,000 R. U. per week.

An interesting clinical observation was the relief of flushes, pruritis vulvae, and vaginal discomfort which coincided with the appearance of the estrogenic effect in the vaginal smear. The author concludes that dihydroxyestrin is absorbed through the skin of human females, as manifested by the production of a characteristic estrogen effect in the vagina.

The Ayala Index. N. Savitsky and M. Kessler. Arch. Neurol. & Psychiat. 39: 988, May 1938.

The value of the Ayala Index as an additional clinical method in the diagnosis of expanding intracranial lesions is discussed. The Ayala index is computed by taking the ratio of the final to the initial pressure and multiplying it by ten. Ten cubic centimeters must always be removed. The Ayala index was determined in 186 consecutive cases of increased intracranial pressure. A low index, below 5.5, is considered in favor of an expanding lesion with probable deformation of the ventricular system. A high index is against the diagnosis of obstructive hydrocephalus. This index was found to be of greatest value in the differential diagnosis of abscess of the brain from otitic hydrocephalus. It has also proved of value in the detection of expanding intracranial lesions which occasionally co-exist with arterial hypertension and cerebrovascular disease. It is an additional diagnostic method and cannot by itself determine the diagnosis in the particular case. It merits further study.

The Creatine Tolerance Test in the Differential Diagnosis of Graves' Disease and Allied Conditions. A. R. Sohval, F. H. King and M. Reiner. Am. J. M. Sc. 195: 608, May 1938.

The creatine tolerance test (Shorr) was performed in a group of patients with one or more of the following conditions: Graves' disease, autonomic imbalance, menopause, hypertension, non-toxic goiter and psychoneurosis. A small percentage of partially positive tests (18%) was encountered in the "non-nervous" control series composed of hypertension, non-toxic goiter and psychoneurosis. A greater incidence of partially positive tests (37%) and a 10 per cent occurrence of completely positive tests was encountered in the group of patients with autonomic imbalance. The greatest frequency of positive tests (90%) was observed in the group with active Graves' disease. Whereas a completely positive tolerance test may be useful in differentiating Graves' disease from a condition which does not at all simulate it, the efficacy of the test in the differential diagnosis of borderline cases, i.e., autonomic imbalance, is sharply curtailed by the following observations:—the occurrence of partially positive tests in control series and of completely positive tests in patients with autonomic imbalance; the occurrence of completely positive tests in only one-half of the patients with active Graves' disease.

The Formation of an Artificial Vagina Without Operation. Robert T. Frank. Am. J. Obst. & Gynec., 35: 1053, June 1938.

Previously the formation of an artificial vagina in cases where malformation was present, necessitated operation. It has been found that the septum between urethra and rectum is so elastic that progressive use of a proper sized plug, applied in the correct direction, in the majority of cases forms an adequate copulatory organ and thus avoids the necessity of an extensive plastic operation.

The Comb of the Baby Chick as a Test for the Male Sex Hormone. R. T. Frank, E. Klempner and F. Hollander. Proc. Soc. Exper. Biol. & Med. 38: 853, June 1938.

Using the 3 day white leghorn chick and making daily topical application for seven days in 0.05 cc. of sesame oil of androsterone to the comb region, both the *sensitivity* and the *uniformity* of comb growth increase was improved. The combined series of 582 chicks permitted the plotting of a characteristic curve which is practically linear. The work is being continued with the object of developing a sensitive, reliable, and inexpensive test for androgens. Quantities as low as 10 gamma of androsterone can be titered ($\frac{1}{10}$ of the accepted international unit).

BOOK REVIEWS

Arthur M. Master, M.D. The Electrocardiogram and X-Ray Configuration of the Heart. Lea & Febiger, Phila., 1939.

The purpose of this book is to emphasize a fundamental aspect of electrocardiographic interpretation that, in spite of its great importance, has been largely neglected in the past. For the first time, the effect on the electrocardiogram of such factors as age, change in body position, respiration, body build, hypertension, valvular disease, pulmonary disease, chest deformities, etc. is considered. The author provides ample proof that changes in the size and shape of the heart, as well as in its position in the chest, produce definite abnormalities in the electrocardiogram which may closely simulate those caused by cardiac disease. The material is presented in atlas form, each case presentation being accompanied by an electrocardiogram and roentgenogram which are excellently reproduced.

The volume is particularly appropriate at this time because the use of the electrocardiograph is becoming very widespread. There is a danger that evidence of myocardial damage will be read into the electrocardiogram on the basis of alterations due to the size, shape and position of the heart.

H. L. J.

Herbert Pollack, M.D., Modern Diabetic Care. Harcourt, Brace & Co., New York, 1940.

This book has been written in recognition of the fact that the education of the diabetic patient is an essential factor in his adequate care. The fundamental principles of carbohydrate metabolism, the calculation of the diabetic diet, the function of insulin and the regulation of the dosage, diabetic hygiene and the usual complications of the disease have been discussed in language intelligible to the average layman. The most important feature of Dr. Pollack's book is the discussion of the therapeutic problems raised by the introduction of protamin zinc insulin. The value of slowly acting insulin has been generally acknowledged but doctor and patient have encountered considerable difficulty in its use. It is the author's opinion that this difficulty is due to two factors (1) the failure to adjust the maximum availability of carbohydrate to the maximum availability of insulin and (2) errors of technique in the administration of protamin zinc insulin. By the use of slowly absorbable carbohydrates, the judicious distribution of fats and proteins and the proper spacing of meals Dr. Pollack has outlined a dietetic regime by which the food intake may be adapted to the retarded absorption of protamin zinc insulin. The proper technique of protamin zinc insulin administration has been described in detail. A chapter on the psychological aspects of juvenile and adolescent diabetes is worthy of note. Recipes, sample menus and tables of food equivalents and substitutions are included in a manual which should prove of value both to the practitioner and his patient.

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CERTAIN NUTRITIONAL DISORDERS OF LABORATORY ANIMALS DUE TO VITAMIN E DEFICIENCY[1]

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In his Welch lecture last October, Dr. Evans (1) presented a masterly review of the current status of the problems centering about the deficiency of vitamin E. It was obviously with some misgiving that I accepted the invitation to speak on a similar topic. However, having yielded to the temptation, I had best concentrate on the pathology of the various disorders which one may with more or less assurance, ascribe to vitamin E deficiency. The chemical aspects of the problems, which are of course the really fundamental ones, I must to my regret, leave to others.

I should like to preface my talk by emphasizing that I am speaking for my colleague, Dr. Marianne Goettsch, as well as for myself. We have been working in close collaboration on these nutritional diseases for the past ten years, and it has been, for me at least, a delightful and profitable association.

I. NUTRITIONAL ENCEPHALOMALACIA OF CHICKS

About ten years ago, Dr. Goettsch (2) and I set out to study the effect of vitamin E deficiency upon reproduction in fowl. We placed day-old chicks upon a simplified diet of skimmed milk powder, casein, lard, cornstarch, cod liver oil, yeast, salts and roughage. They throve nicely for the first three weeks or so, and then began to show a variety of symptoms pointing to some grave disorder of the central nervous system,—tremors, forced movements, head retraction, muscular weakness, somnolence. These symptoms often came on very suddenly, and many of the chicks died; some, however, recovered and as we became more familiar with the disease, we found many instances in which the symptoms were transient or even imperceptible, and yet definite lesions were found when the animals were killed. The incidence of the disease in several thousand chicks on our experimental diet has been about sixty per cent, and we have not succeeded in finding out why all the birds did not succumb. We have tried four different breeds and all are equally susceptible. But as the chicks grow older, the incidence becomes progressively less, and the adult bird is completely resistant.

[1] Delivered at The Blumenthal Auditorium, The Mount Sinai Hospital, New York City, May 14, 1940 as part of the Symposium on Vitamins.

The underlying pathology of this disease proved to be interesting. The cerebellum was most often affected, then the cerebrum, less often the mid-brain and medulla. The essential lesion is an ischemic necrosis—often so extensive as to destroy four-fifths of the cerebellum of one or both hemispheres. Necrosis of ganglion cells, oedema, hemorrhages, and the constant finding of hyaline thrombi in the small vessels—these were the characteristic features, which pointed unmistakably to a circulatory blockage as the cause of the lesions. Ink or dyestuff could not penetrate the affected areas even in the earliest stages. However, we have never been able to determine whether the vascular occlusion was primarily functional or due to the capillary thrombi.

In chicks which survived this acute phase of the disease, reparative changes occurred—gliosis, new growth of blood vessels and reticulum fibers, and calcification. Such spontaneous healing, even in the absence of supplemental treatment with vitamin E, is comparable with the spontaneous recovery which occurs in young rats with muscular dystrophy due to vitamin E deficiency. There appears thus to be a critically susceptible period.

We did not at once recognize this nutritional encephalomalacia of chicks as a manifestation of vitamin E deficiency, in spite of the fact that our experimental diet was purposely lacking in this factor. We were led astray by the observation that a diet of natural foods in which vitamin E had been destroyed by treatment with ethereal ferric chloride after the method of Waddell and Steenbock (3) failed to evoke the disease; also the addition of various foods, supposedly rich in this factor, did not always afford protection. We were further influenced by the current view that vitamin E was concerned primarily, and as was then believed, exclusively, with reproduction. It turned out that we were wrong. The chicks could be regularly protected by a variety of vegetable fats when these were substituted for an equivalent amount of lard in diet 108. The activity was found to reside in the non-saponifiable fraction of the alcoholic extracts, even after removal of the sterols, and a very considerable concentration of the active factor was thus effected. Following the chemical isolation of vitamin E by Evans, Emerson and Emerson (5) in 1936 and its identification as α-tocopherol, it was an obvious experiment to test its efficiency in the prevention of this disease. This has been done by us (6), and independently by Dam, Glavind, Bernth and Hagens (7)—indeed the publicational priority belongs to those workers. It has been found that complete protection may be obtained by the daily administration of 0.2 mg. of either the natural or the synthetic α-tocopherol or the tocopherol acetate. It is of course possible that other tocopherols, or their derivatives may prove effective, but this has not yet been tested. The observation that the protective effect of natural foods against encephalomalacia is not destroyed, even when the anti-sterility factor is rendered

ineffective by ethereal ferric chloride treatment, also demands further explanation. Ni (8, 9) has also obtained partial protection by the addition of 2 per cent donkey skin gelatin (Ah-Chiaco) to an encephalomalacia-producing diet, but the protective factor in this substance has not been chemically defined.

It was interesting to find that this chick disease, manufactured in the laboratory, had its counterpart in the field. "Crazy chick disease," as it is called, had been familiar to New England farmers for a number of years. Its identity, as far as symptoms and lesions are concerned, with the experimental encephalomalacia, was established by Jungherr in 1936 (10), and by others since. There is little reason to doubt that it will be found to be preventable by proper dietary supplement.

Before leaving the subject of vitamin E deficiency in chicks, I should refer to the recent paper of Dam and Glavind (11) on "Alimentary Exudative Diathesis." An extreme subcutaneous edema appeared in some of their chicks, and this they regard as a characteristic manifestation of vitamin E deficiency, indeed, suggesting that it might afford a method of biological assay, since it was preventable by wheat germ oil and by α-tocopherol. In our monograph on "Encephalomalacia" (Bull. 229 of the Stoors Agr. Exp. Station), we have noted the rare occurrence of edema—most often as was the case in the experiments of Dam and Glavind on a low fat diet. It was seen but once on diet 108, and there was no correlation between the generalized edema and the cerebral lesions.

II. NUTRITIONAL MYOPATHY OF DUCKLINGS

When the encephalomalacia-producing diet 108 was tried on ducklings, it produced effects quite different from those found in chicks (12). Clinically, the chief symptom was muscular weakness, so extreme in the last stages, that the animals could not stand erect, or even hold their heads up from the table. Symptoms of brain injury, such as tremors, forced movements, coma, etc., were never observed. And indeed, in the duckling, the brain and other parts of the central nervous system were found to be unaffected. The skeletal muscles, however, showed definite lesions. There was hyaline necrosis of the fibers with rupture and segmentation, followed by a cellular reaction of leucocytes and histocytes, and attempts at regeneration by the activated myoblasts. The lesions are thus practically identical with those produced in guinea pigs, rabbits and young rats by vitamin E deficient diets. Although we have obtained protection with Crisco and partial protection with the non-saponifiable fractions of soy bean oil, the crucial experiment with α-tocopherol has not yet been carried out. This laboratory disease also proves to have its counterpart in the enzoötic muscular dystrophy of ducklings described by Seifried and Heidegger (13) in Bavaria.

III. NUTRITIONAL MYOPATHY OF THE GIZZARD IN TURKEYS

The turkey reacts to vitamin E-deficient diets in a very individual manner. The nervous system and skeletal muscles escape; it appears to be the smooth muscle of the gizzard, as Jungherr first observed, which is peculiarly vulnerable. There appears a patchy hyaline necrosis of the smooth muscle fibers, attended at first by an acute inflammatory reaction, and followed later by fibrosis and attempts at regeneration of the muscle fibers. Dr. Jungherr and I (14) have been able to lower the incidence of the disease by administering soy bean oil or wheat germ oil, but have not as yet tried out α-tocopherol.

Similar lesions have been found in young turkey poults obtained from commercial hatcheries.

IV. NUTRITIONAL MUSCULAR DYSTROPHY IN GUINEA PIGS AND RABBITS

The generalized degeneration of the muscles in these animals, for which Dr. Goettsch and I suggested the term—nutritional muscular dystrophy, was first observed by us in 1931 to develop following an ethereal ferric chloride-treated scorbutic diet supplemented by adequate amounts of orange or tomato juice (15). Since then, it has been studied by a number of other workers—among whom I may mention Morgulies and Spencer (16); Ni (17); Woodward and McKay (18); Chor and Dolhart (19); Shimotori, Emerson and Evans (20); Mackenzie and McCollum (21); Morris (22); and Madsen (23), who have found little difficulty in producing the disease. Although the course, duration and intensity vary considerably in individual animals, their clinical behavior is on the whole quite characteristic. After a period of normal growth, which may range from two weeks to six months or more, there is an abrupt cessation, followed usually by a precipitous decline in weight. The animals become lethargic, and develop increasing muscular weakness to the point of almost complete helplessness, so that they cannot right themselves when placed on their back, and cannot reach their food pans. In this state, they die, and we have never observed spontaneous recovery.

The skeletal muscles throughout the body are found to show extreme lesions, which however are not usually symmetrical, and do not of necessity affect a muscle in its entirety. Both the gross and microscopic appearances depend upon the duration and intensity of the lesions. In the very early and acute stages, which may develop within a few hours, the muscles are somewhat pale and watery, and the contractility is lost. Microscopically, there is extreme hyaline necrosis and fragmentation of the fibers, as well as much interstitial edema. Very soon, however, there is a violent cellular reaction. The necrotic fibers become invaded by polymorphonuclear leucocytes and by histocytes which often fuse to form plasmatic multinucleate masses about the necrotic remnants. These

may become calcified. Particularly in young animals, the muscle nuclei, which escape destruction, early become activated. They divide mitotically, arrange themselves in rows; new myofibrils are formed on the surface; the cytoplasm which at first stains purplish, becomes red as the myohemoglobin is regenerated. This regeneration is sometimes extraordinarily active, even while the degenerative alterations are in full blast.

The dystrophic changes are not always so fulminating as I have depicted them; and the disease may run a chronic course. In such animals, comparatively few fibers are destroyed at any one time, but their gradual loss and replacement by fat and fibrous tissue brings about a picture which is identical with that of an advanced case of human muscular dystrophy. Such animals may survive for many months, dying finally of inanition or of a terminal pneumonia. There are several points in the pathology which I should like to stress. One is the excellent preservation of neurites and end-plates in the midst of the necrotic muscle cells (21). With Dr. Wolf's assistance, we have studied the brain and spinal cord quite thoroughly in some of our animals, and have seen no alterations which seemed to be of significance.[2] The histological evidence, therefore, favors a primary muscular lesion, rather than a neural one.

Another point is the striking selectivity of the lesions for the skeletal muscles. Madsen (23), working in our laboratory, found degenerative changes in the heart muscle of a few rabbits and guinea pigs, but I am not wholly convinced that these lesions are referable to the vitamin E deficiency. They are certainly not a usual finding in this disease. The smooth muscle is never affected.

Most of the animals die before the age of sexual maturity, and we have not been able to study the effect of vitamin E deficiency upon reproduction in the rabbit or guinea pig. One of our rabbits, however, gave birth to two young while she was still in the incipient stage of the disease as shown by biopsy. The young were scrawny and weak, and survived but a day. Their muscles were found to show extreme degeneration, so that the development of the disease in utero was certain, and the normal transference of vitamin E to the embryo through the placenta may be assumed.

Since the preliminary report of this observation in 1936 (25), we have been able to study 20 young born of mothers maintained on diet 48 in which 8 per cent of soy bean oil was substituted for the lard in diet 11. This sufficed to protect the mothers against muscle dystrophy for periods up to 958 days. It was not sufficient, however, to prevent the development of muscle dystrophy in the offspring during late intra-uterine or early post-natal life. Sixteen of the twenty young, born dead or surviving less

[2] Ekblad and Wohlfart (Ztsch. f. I. Ges. Neurol. u. Psych.: 168: 145, 1940) have recently described sclerotic changes in the ganglion cells of the spinal cord. These have not been present in our material.

than 5 days, showed lesions of varying intensity in the muscles. The remaining four with normal muscles were all first litter animals.

An interesting feature of the disease in newborn rabbits is the accompanying edema of the subcutaneous tissue and intramuscular connective tissue, which is perhaps analogous to the "exudative diathesis" regarded by Dam and Glavind as a manifestation of vitamin E deficiency in the chick.

There is also an analogy to the muscular dystrophy of young rats born of mothers partially deprived of vitamin E, with this difference that in the rabbits, the disease is present at birth, while in the rats it appears only at the end of lactation.

What is the evidence that this muscle disease of rabbits and guinea pigs is really a manifestation of vitamin E deficiency? This question was discussed very thoroughly by Dr. Evans in his Welch lecture. The evidence in favor of this view is accumulating. In our original paper, Dr. Goettsch and I thought that we could eliminate the lack of vitamin E as a factor in the causation of the disease, since daily doses of approximately 200 mg. of tested wheat germ oil failed to protect guinea pigs. In addition guinea pigs and rabbits upon the diet which had not been treated with ethereal ferric chloride, and contained vitamin E in amounts adequate for normal reproduction in rats, eventually developed dystrophy. In the light of subsequent work, it would seem that the dosage, upon the particular diet used (containing lard and cod-liver oil) was probably inadequate. Mackenzie and McCollum (21), using the creatin excretion as a criterion of the disease have obtained curative effects with α-tocopherol; Morris (22), with doses of 18 to 25 mg., obtained definite symptomatic cures; Shimotori, Emerson, and Evans (20) effectively prevented the disease in guinea pigs over a period of 200 days by supplementing the diet with 3 mg. of synthetic α-tocopherol on alternate days. Dr. Goettsch and I have also succeeded in producing remissions and in a few instances permanent cures in guinea pigs by feedings or injections of 20 to 25 mg. of synthetic α-tocopherol. The progress of the disease in our animals was followed by repeated muscle biopsies, and we were amazed to find that severe lesions may completely disappear within a week following the injection or feeding of a single dose. The evidence then supports the view that vitamin E deficiency is the essential thing in the causation of this disease, and does not substantiate the contention of Morgulies (24) that there is an additional water soluble factor (B_4?) concerned.

The point of view advocated by Madsen, McCay and Maynard (27) that the toxicity of cod-liver oil for the herbivora is the essential factor in the production of muscular dystrophy, can not, we think be maintained in the face of Cummings and Mattill's (28) demonstration that cod-liver oil brings about the oxidative destruction of vitamin E. The more recent findings of Davis, Maynard and McCay (29) show that the addition of

3 per cent cotton-seed oil to a synthetic dystrophy-producing diet prolongs and in some cases prevents the disease. This finding can also be explained by the vitamin E content of the vegetable oil.

A rather instructive illustration of the effect of cod-liver oil in precipitating muscular dystrophy was brought to our attention by Dr. Leonard Goss of the Bronx Zoological Garden (30). Four tree-kangaroos were placed on exhibition at the World's Fair, and to make them especially presentable, they were given large amounts of fish liver oil. They sickened, and three of them died, with extreme muscular dystrophy. The third one was brought back to the Bronx Zoo, but continued to show muscular weakness in spite of the withdrawal of fish liver oil from the diet. He was then given α-tocopherol and made a rapid and spectacular recovery.

V. MUSCULAR DYSTROPHY IN YOUNG RATS

This chapter of the story begins with the report of Evans and Burr (31) in 1928, that the offspring of female rats, partially depleted of vitamin E, often became more or less completely paralysed towards the end of lactation. Some of their rats died, others recovered, with or without residual weakness. But it was not until the publication of Olcott's paper in 1936 (32) that the pathology underlying these symptoms was made clear. Olcott found widespread necrosis of the skeletal muscles lesions essentially like those in the more acute phases of the muscular dystrophy of rabbits and guinea pigs. We have confirmed and perhaps amplified Olcott's observations (32), as have Telford, Emerson and Evans (34). The disease often develops with almost explosive suddenness; and what to us seems very remarkable, it appears to be self-limited if the young rats survive. Even without any vitamin E supplement, healing of the muscle lesions occurs with astonishing rapidity, so that after a week, little trace of the original devastation can be found. This is one of the interesting problems in connection with this curious disease that remains to be investigated.

As was the case with the chicken encephalomalacia, the symptoms are not always a reliable criterion. We frequently find extensive muscle lesions in rats killed on the 24th or 25th day. These rats have shown none of the usual symptoms such as clenching of the paws, rough fur, bloody crusts about the eyes, and paresis.

Dr. Goettsch and Dr. Ritzmann (35), modifying Evan's original procedure slightly, have induced the muscle disease in a high percentage of rats. There appear, however, to be individual differences in the amount of vitamin required by the mother rat to protect her children against the disease, and these constitutional differences which may conceivably have a bearing upon the incidence of muscle dystrophy in humans, are being studied further.

Although our own studies have been restricted almost entirely to young

rats, others have found lesions both of the muscles (Knowlton and Hines) (36) and of the spinal cord (Einarson and Ringsted) (37) in older rats maintained for several months on a vitamin E-deficient diet. The studies of the Danish observers are of particular interest inasmuch as the degeneration of the pyramidal tracts and anterior cells, as well as of the dorsal sensory tracts, offer a resemblance to the lesions of amyotrophic lateral sclerosis in man. In two of a number of our older rats, Dr. Wolf has found similar changes. The therapeutic results recently reported by Dr. Wechsler (38) and Bicknell (39) in England at least offer the hope that the analogy between the rat and the human disease is not a superficial one.

It is now well established through the work of Evans and Burr (31), of Morelle (40), of Barrie (41), of Demole and Pfaltz (42), of Goettsch and Ritzmann (35) and of Knowlton, Hines and Brinkhous (43) that this muscular dystrophy of young rats is effectively prevented by wheat germ oil, and by α-tocopherol, either natural or synthetic. A single dose of 0.5 mg. administered on or before the 17th day regularly confers protection. Oil of wheat germ treated with ethereal ferric chloride, was still anti-dystrophic in spite of the fact that 20 gm. failed to prevent resorption in vitamin E depleted rats, and this discrepancy invites further study.

In the hope of learning something further of the pathogenesis of the muscle lesions, we have during the past winter, performed some rather interesting though childishly simple experiments (44).

The sciatic nerve to the left leg was resected and the histological lesions of the gastrocnemius muscle on the two sides were compared. It was found to our surprise that the dystrophic lesions did not develop in the muscle deprived of its nerve supply when the operation was performed at any time between the 5th and the 17th day. When, however, the nerve was cut on the 18th day, the protection was no longer effective—either because the irritability of the distal segment persisted for a day or two, or because the changes initiating the muscle necrosis were already under way, although there were at the time no visible symptoms or gross lesions (table 1).

These results seemed to inculpate some obscure nervous influence in the production of the lesions. We have had the thought that the necrosis might be the result of angiospasm. The persistence of a shell of intact fibers on the surface of the muscle suggested that they might have been spared because of an additional blood-supply from the fascial vessels. Loss of sympathetic innervation through section of the sciatic nerve might then have inhibited the vasoconstriction causing the necrosis.

This pretty idea received a rude shock when we found that section of the Achilles tendon leaving the nerve supply intact, was equally effective in protecting the gastrocnemius (table 2). It is, therefore, not the loss of nerve supply *per se* which is essential, but rather the loss of muscle tonus, that affords protection. We have found further that mere in-

activity of the muscle is not sufficient to prevent the lesions. We placed one hind limb in a molded copper splint completely immobilizing the knee and tibio-tarsal joints in the extended position. Since the mother rat resolutely opposed this procedure, and tore off the splints, it was necessary to feed the young rats on skimmed milk with a dropper. The splinting

TABLE 1

Effect of section of left sciatic nerve upon muscular dystrophy of young rats on vitamin E deficient diet

SERIAL NUMBER	LITTER NUMBER	AGE AT OPERATION	AGE AT DEATH	LESIONS		
				R. gastrocnemius	L. gastrocnemius	Other muscles
		days	*days*			
1	234 a	5	21	++++	−	++++
2	199 a	7	22	++++	−	++++
3	200 a	12	19	++++	−	++++
4	200 c	12	20	++++	−	++
5	189 a	15	16	±	−	−
6	189 b	15	18	+ (?)	+++ (?)	++++
7	196 a	15	20	+++	−	+++
8	196 b	15	20	+++	−	+++
9	196 c	15	24	++++	−	+++
10	196 e	15	24	±	−	−
11	196 g	15	22	+++	−	−
12	196 h	15	22	+++	−	−
13	196 i	15	23	+	−	−
14	218 a	15	24	±	−	+
15	218 b	15	23	+++	−	+++
16	218 c	15	24	+++	−	+++
17	218 d	15	23	+++	−	+++
18	240 a	16	21	++++	+	++++
19	240 b	16	21	++++	−	++
20	217 a	17	19	++++	−	+++
21	217 b	17	22	++++	−	+++
22	216 a	17	25	++++	−	++++
23	224 a	18	20	+++	+++	+++
24	224 b	18	20	+++	+++	+++
25	224 c	18	20	+++	+++	+++
26	224 d	18	25	+++	+++	+++
27	224 e	18	25	−	+++	+++
28	244 a	18	20	++++	++++	++++
29	244 b	18	25	++++	−	−

did not protect, and lesions were found on both sides. The effect of transection of the spinal cord at the lower dorsal or upper lumbar levels was also studied in a fairly large series, but the effects as regards the muscles of the lower extremities were not consistent, probably because of the varying extent of the destruction of the cord below the level of the section.

The interpretation of such experiments is not easy, and it is obvious that much further work must be done before we can even guess at the precise rôle which vitamin E plays in muscle physiology. That the denervated or tenotomized muscle is less sensitive to the lack of vitamin E than the functionally active muscle, seems proven. But we do not know why, and have not been able, as yet, to formulate a plausible hypothesis.

One is tempted to conclude a lecture of this sort with some sweeping generalizations. But it is pretty obvious that we are only at the beginning

TABLE 2

Tenotomy of left gastrocnemius

SERIAL NUMBER	LITTER NUMBER	AGE AT OPERATION	AGE AT DEATH	LESIONS		
				R. gastrocnemius	L. gastrocnemius	Other muscles
		days	*days*			
1	239-4	10	24	++++	±	++++
2	239-5	10	24	+	−	±
3	239-6	11	24	++++	−	++++
4	211-5	14	19	++	−	+++
5	216-1	16	21	++++	++++	++++
6	216-6	16	21	++++	−	++++
7	216-4	16	22	++++	−	++++
8	254-2	17	25	++	−	+++
9	254-4	17	25	++++	−	++++
10	255-5	17	25	++++	−	++++
11	254-7	17	25	++++	−	+++
12	258-6	17	25	++++	−	++++
13	258-7	17	21	++++	−	++++
14	258-8	17	24	++++	−	++++
15	258-9	17	25	++++	−	++++
16	258-10	17	25	++++	−	++++
17	234-1	17	23	++	−	++++
18	234-2	17	25	++++	−	++++
19	234-4	17	18	++	−	++++
20	234-5	17	24	++++	±	++++

of our knowledge as to the fundamental rôle which the tocopherols and related substances play in nutrition. As to the applicability of results obtained with laboratory animals to problems of human disease, one can make no forecasts, but the work has gone far enough, it seems to me, to justify a cautious empiricism. The fact that a partial deficiency of vitamin E in the mother may manifest itself only in the offspring, seems to me to be one of the most significant lessons that one can draw from this work. May not similar things happen in human diseases, and help to explain the supposed hereditary or familial character of certain nervous and muscular disorders?

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TERMINAL ILEITIS

Clinical Recovery without Operation Four Years after Onset

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Terminal or regional ileitis, a malady sharply defined by Crohn, Oppenheimer and Ginzberg (1) from the broad group described by Moschcowitz and Wilensky (2) under the designation of "Non-specific Granulomata of the Intestine," has, with keener recognition, proved to be a more common lesion than originally regarded, so that in the fairly extensive literature that has accumulated in the past few years, the clinical and the morbid anatomy of this disease has been considerably clarified. Much is still unknown, and the two major issues that await solution are, first, the cause, and second, the biological history of the disease. It is in respect to the second issue that this communication is contributed.

CASE REPORT

History (Adm. 385295). J. E., male, aged 15, was admitted to The Mount Sinai Hospital on October 5, 1935. His family history was irrelevant. He had suffered from hay fever for the preceding four years. Two years previous to admission he began to have attacks of pain in the lower abdomen, with loss of weight, anorexia, and occasional nausea and vomiting. After six months the abdominal pains disappeared but the anorexia and loss of weight continued.

Examination. The boy appeared much younger than his chronological age. The parenchymatous organs were normal.

Laboratory Data. The hemoglobin was 70 per cent; the white blood count, 5,600, with 62 per cent polymorphonuclear neutrophiles and 38 per cent lymphocytes. The blood pressure was 100 systolic and 70 diastolic. The urine was normal and blood Wassermann reaction was negative. The blood calcium was 10 mg. per 100 cc.; the cholesterol, 140 mg. per 100 cc.; the total blood protein was 6.2 per cent, of which the albumin fraction was 3.6 per cent. The stools were liquid and gave a 4 plus guaiac reaction. The von Pirquet and Mantoux reactions were negative. The stool culture showed bacillus coli on culture, and a slight bacteriophage for the Mt. Desert strain of dysentery bacillus. A Janney test showed a flat curve. The Rehfuss test meal showed a normal curve. Sigmoidoscopic examination revealed a normal mucosa. A gastro-intestinal x-ray examination showed a diffuse ulcerating lesion in the distal half of the jejunum and the terminal six or seven inches of the ileum. Between these two lesions, the bowel was normal. The jejunum was narrow and irregular and there was absence of the normal mucosal markings which were replaced by a polypoid pattern. The appearance of the ileum was that seen in regional ileitis (fig. 1). An x-ray examination of the colon revealed no abnormality. He was regarded by the endocrinologist as a mild case of endocrinological disturbance of the Lorain-Levy type. An x-ray examination of the skull showed a normal sella turcica.

Course. His highest temperature during his stay was 100.6°F. His weight

FIG. 1. A diffuse ulcerating lesion involving the distal half of the jejunum and the terminal six to seven inches of the ileum. Between these two lesions normal bowel was present. The jejunum is narrowed and the normal mucosal workings are replaced by a polypoid pattern.

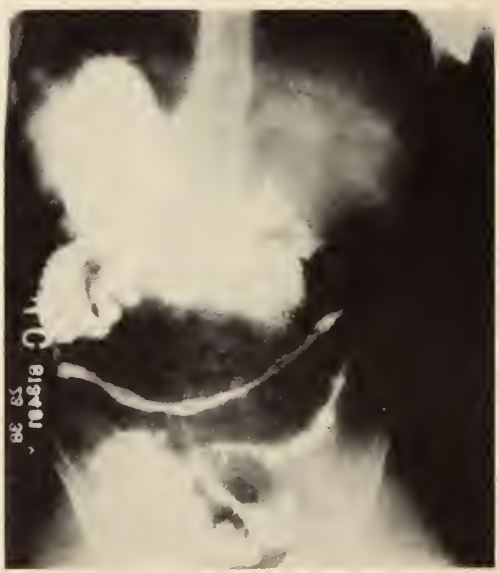

FIG. 2. Appearance four years later showing little change as compared to earlier findings.

on admission was 99 pounds, and on his discharge, three weeks later, 95 pounds. He was advised to go on a high calory, low residue diet.

He returned on numerous occasions for follow-up study. On January 20, 1936, he weighed 94 pounds. On June 15, he weighed 89 pounds and he complained of noeturnal, colicky, abdominal pains sufficient to awaken him. An x-ray examination revealed the same findings in the jejunum and ileum as before. In September, 1936, he complained of abdominal cramps and bloody diarrheal movements during the past week. On February 15, 1937, he complained of occasional slight abdominal pain but he had maintained his weight. On September 19, 1938, he showed a gain of eleven pounds. He asserted that he felt perfectly well, that his bowels moved onee daily, and that the stools were firmer. An x-ray examination revealed the proximal portion of the jejunum to be normal. The distal portion for a distanee of twenty-five inches was markedly contracted. The margins were irregular and there was evidence of a small-sized polypoid formation. The distal portion of the ileum was also markedly constricted, irregular, and had the typical appearance seen in regional ileitis (fig. 2).

SUMMARY

A boy of 18, atrophic and undersized, with a Lorain-Levy type of dyspituitaryism, presented the typical clinical and roentgenological evidences of terminal ileitis and jejunitis of approximately five years' duration. On a dietary regime alone, he is at present clinically, but not anatomically, well. There is still roentgenological evidence of narrowing of the gut and polypoid formation in the jejunum and ileum.

DISCUSSION

Terminal ileitis is usually a disease of many years' duration. The treatment of choice is, of course, operation, preferably a complete resection of the affected area. The results with this treatment thus far, as exemplified in the 32 cases reported by Dr. A. A. Berg, are excellent. There is no other specific treatment of the disease that is of any avail. What occurs then in unoperated cases, or, in other words, what is the life cycle of the disease? Inasmuch as my experience with a "follow through" is limited, it is wise to call upon the observations of Crohn (3) whose observations are much more extensive. Of eighteen unoperated cases, three died, all of peritonitis and exhaustion. Another case required resection after two years because of progressive deterioration with fever, mass formation, diarrhea and obstruction. Four of Crohn's cases are apparently doing well, gaining weight, with only a slight tendency to diarrhea. Another four are apparently not improving, and, in Crohn's opinion, will eventually demand operation. The remaining six cases have disappeared from observation. As Crohn insists, the number of cases is too small and the period of observation too short to permit broad generalizations concerning the life cycle of the disease. This matter must remain for the next generation of observers. I have had the privilege of observing two cases over a prolonged period, the first for twenty-one years, the second for twelve.

The first patient, aged 18, was one of the four reported by Moschcowitz and Wilensky under the title of "Non-specific Granulomata of the Intestine." He had originally undergone a resection of the intestine and subsequently four operations for attacks of peritonitis. He had had no operations for the past fifteen years. He still has three to four fluid movements daily, but he has maintained his weight and is now a middle-aged man, married, and pursues a rather strenuous business. He is on a low residue diet and takes *tr. opii deod.* up to ten drops three times daily. The second patient was a woman 35 years of age, on whom the late Dr. Walter M. Brickner performed an intestinal resection for terminal ileitis twelve years ago. About a foot of intestine was resected. Soon after the operation the diarrhea returned so that it was surmised that a segment of diseased intestine was still present. Although she felt fairly well for the next ten years, the persisting diarrhea forced her to undergo another resection by Dr. A. A. Berg three years ago. Since then she has been completely well.

The clinical similarity between terminal ileitis and tuberculosis is striking. While clinical healing, as in the case I have reported, is possible, anatomical healing in the sense of a complete *restitutio ad integram* is highly improbable. In both, a relighting of the morbid process is always possible. In this sense, as in tuberculosis, we cannot speak of a cure but only of an arrest of the anatomical process.

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CASE ILLUSTRATING THE TREATMENT OF BILATERAL RENAL CALCULI, INCLUDING PARATHYROID EXPLORATION[1]

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The therapeutic management of a patient with bilateral, multiple, or dendritic calculi is one of the most difficult tasks confronting the urological surgeon. The following case is presented for purposes of illustration and discussion of some of the problems involved.

CASE REPORT

History (Adm. 451072). C. B., a 45-year old housewife, was admitted to The Mount Sinai Hospital on August 4, 1939 and discharged on November 9, 1939. Her history was essentially negative except for an attack of left loin pain and cloudy urine five years before admission, at which time she was told that she had stones in both kidneys. The stones were said to have been too large for removal and operation was not advised. Eight months before admission, she had mild dysphagia and three months before admission some enlargement in the region of the thyroid gland had been noted. Lately, there had been a painless swelling of the abdomen and a moderate weight loss, but no urinary symptoms. Weakness and lassitude were prominent symptoms. The patient had had two pregnancies with normal deliveries.

Examination. The patient was pale, undernourished and obviously chronically ill. She had a slight exophthalmos, and a mild tremor of the hands. There was a firm, cherry-sized nodule in the lateral aspect of the right lobe of the thyroid gland. The heart and lungs were negative but the pulse rate averaged 116 per minute. The right half of the abdomen was moderately distended and protuberant. A large, smooth, non-tender mass was palpated in the right flank, apparently the right kidney. The left kidney was not palpated.

Laboratory Findings. Blood count: hemoglobin, 52 per cent; red blood cells, 3,810,000; white blood cells, 7,500 with a normal differential. The blood pressure was 110 systolic and 70 diastolic. The sedimentation time was 7 minutes. The basal metabolic rates were plus 16 and then plus 2 volumes per cent. The electrocardiogram was normal. The bladder urine examinations showed albumin, one plus; sugar, none; and much pus on microscopic examination. The urine culture showed B. proteus to be present. The maximum specific gravity of the urine was 1016. The blood urea nitrogen was 13 mg. per cent; sugar, 110 mg. per cent; calcium, 9.8 mg. per cent; and phosphorus, 3.1 mg. per cent. The blood total protein was 6.9; albumin, 4.4; and globulin, 2.5 milligrams per 100 cubic centimeters. The blood phosphatase determinations on three occasions were 15, 25, and 22 King-Armstrong units respectively. After a short period of observation on the medical service, the

[1] Presented before the Monthly Urological Conference, December 13, 1939.

urological status was investigated. X-ray examination of the abdomen showed a large right kidney with multiple and dendritic calculi, and a left kidney the upper portion of which was filled with multiple calculi. On the excretory urogram only a segment of the upper left ureter and a segment of the bladder were visualized (fig. 1). On cystoscopic investigation, the right kidney was found to have no function. Tapes of thick pus were seen emerging from two right ureteral orifices which immediately joined to form a single right ureter. No indigo-carmine was excreted from this side. From the left kidney, clear urine with good indigo-carmine excretion was collected. On culture of the left kidney urine, B. proteus was recovered.

After preparation by means of several transfusions, the patient's right lumbar region was explored (September 19, 1939). Avertin, ethylene, and ether were the anesthetics used. A right subcapsular nephrectomy (G. D. O.) was performed.

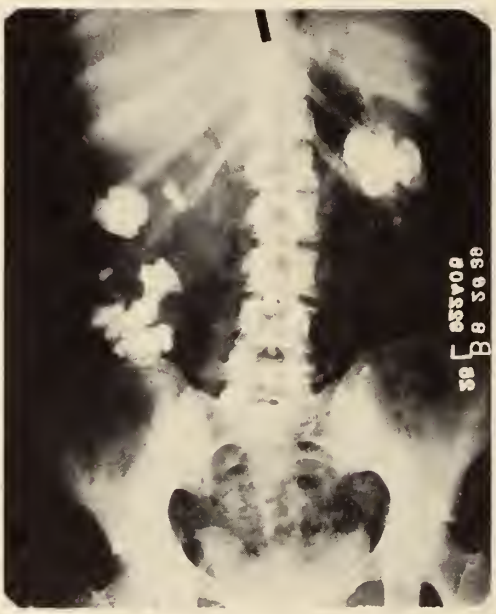

FIG. 1. Intravenous urogram, 25 minute plate. Multiple and dendritic stones in right kidney. No function. Left kidney: dendritic and multiple stones in upper pole. Dye in left ureter and bladder.

The kidney was huge and fixed by extensive perinephritis. After its removal, large gauze drains were placed in the resultant cavity and the wound partially closed. The kidney was found to be a large, multilocular pus sac filled with large, irregular stones and gravel which crumbled on being touched. Very little renal tissue was grossly discernible. The pathological report (#67821) was "Chronic and acute calculous pyonephrosis. Ureter showing chronic ureteritis and peri-ureteritis."

The chemical analysis of the stones showed the presence of calcium carbonate and ammonium magnesium phosphate.

The patient made an uneventful postoperative convalescence. There was a moderate purulent discharge from the wound which rapidly cleared up. Because of the low hemoglobin, another transfusion was given.

After about three weeks, the patient's general condition was excellent and she

was returned to the medical service for investigation of a possible disturbance of the calcium metabolism. An x-ray examination of the skull (fig. 2) had shown changes roentgenologically consistent with hyperparathyroidism, Paget's disease, or metastatic malignancy. The X-ray report stated that "the examination of the skull shows rounded areas of increased density alternating with areas of decalcification in the calvarium suggestive of metastatic malignancy or hyperparathyroid disease. The possibility of Paget's disease is not entirely ruled out, although the absence of findings in the bones of the pelvis and lumbar vertebrae and lack of increase in thickness of the cranial vault make this diagnosis unlikely. Advise examination of other bones." All the bones were then examined by X-ray but were found to be normal.

Calcium balance studies with the patient on a 100 mg. daily calcium intake preoperatively had revealed a total urinary excretion of 650 mg. for three days. This

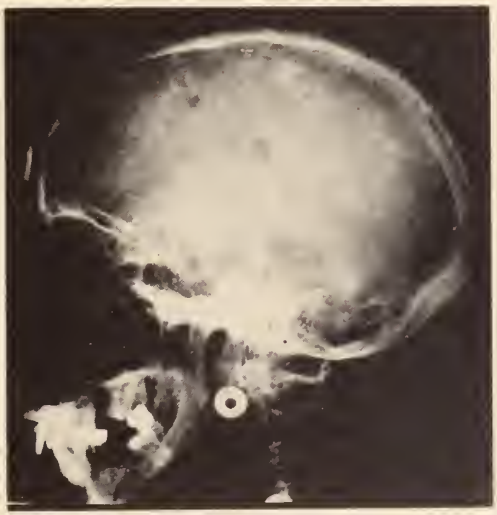

FIG. 2. Roentgenogram of the skull. Note areas of increased density and rounded areas of decalcification.

was repeated and the total excretion was found to be 415 mg. for the three days. Both these levels were abnormal, the upper limits on such a diet usually being 200 mg. excretion for three days.

A diagnosis of possible hyperparathyroidism was made on the following evidence: 1) Long history of bilateral renal calculi with the presence of calcium and phosphate stones; 2) suggestive bone changes in the skull; 3) elevation of blood phosphatase on three occasions (15, 25, 22 King-Armstrong units); 4) two elevated urinary calcium excretion tests on a three-day 100 milligram daily intake (650 and 415 mg).

An exploration of the parathyroid glands was performed on November 1, 1939, by Dr. J. H. Garlock, under ethylene anesthesia. No tumor was found and four normal parathyroid glands were visualized. The nodule in the right lobe of the thyroid, previously correctly diagnosed as a thyroid adenoma, was removed. The convalescence from the operation was prompt and uneventful.

Before final discharge from the hospital the patient still had purulent bladder urine infected with B. proteus which was uninfluenced by a short course of sulpha-

nilamide therapy. She was discharged to a convalescent home and will re-enter the hospital shortly for surgical care of the remaining left kidney.[2]

COMMENT

While the evidence tabulated above favored a diagnosis of hyperparathyroidism, it was realized even pre-operatively that there were contradictory data; namely, the absence of generalized skeletal osteoporosis, and the absence of hypercalcemia and hypophosphatemia. However, inasmuch as parathyroid exploration is a really innocuous procedure, it was felt that nothing would be lost by exploring the neck, whereas much could be gained by the discovery of a parathyroid adenoma and its removal.

The elevation in phosphatase was possibly associated with the bony changes in the skull (early Paget's disease?). On the other hand, it is unusual to see such high phosphatase levels with such limited bone changes.

The explanation of the elevated urinary calcium excretion is not clear. Gravel from the kidney might affect these determinations, although there is no evidence that the patient passed gravel at the time of these tests. In this connection, Flocks (4) has recently published studies which show that patients with renal calculi can have a high urinary calcium excretion without any clinical evidence of hyperparathyroidism. In fact, of thirty-five patients with renal calculi a high urinary calcium excretion was found in twenty-three. Only two of these patients had hyperparathyroidism.

Calculus formation incident to the hyper-excretion of crystalloids, as stressed experimentally by Keyser (7), using oxamide, is best illustrated in humans in the cases of hyperparathyroidism. Although the work of the Boston group (Albright et al. (1–2)) in stressing the occurrence of renal calculi in hyperparathyroidism has been a great stimulus to the study of renal calculi, the frequency of this particular association is low. In an early series, 27 per cent of eighty-three patients with hyperparathyroidism had renal calculi (1). In a recent communication, Chute (3) reports that 83 per cent of thirty-six patients with hyperparathyroidism had renal calculi. He states, however, that hyperparathyroidism is a rare disease and that it is the cause of about 3 per cent of the cases of kidney stone. Unfortunately, in this institution, we have rarely found any suggestive evidences of hyperparathyroidism in the many cases of lithiasis of the urinary tract which have been observed. Garlock (5), with an experience of over forty parathyroid explorations, has had approximately twenty-two cases of removal of parathyroid adenomata for osteitis fibrosa

[2] Since this case was submitted for publication, the patient was re-admitted to the hospital. An exploratory left renal operation was performed, following which the patient died with sepsis and chronic and acute pyelonephritis. At autopsy no abnormal parathyroid tissue was found. The left kidney presented an unusual and interesting anomaly which will be reported in detail at a later date.

cystica. In only one of the latter cases were renal calculi present and in three others only small calcifications were demonstrated in the region of the kidneys. Confirming our experience is a published study (6) of 1,206 cases of urolithiasis in which hyperparathyroidism as an etiologic factor was found in less than 0.2 per cent. The presence of secondary parathyroid hyperplasia in the cases of renal calculi with marked renal insufficiency and secondary bone changes is now well-known (2) and is only mentioned for differentiation from the primary types. It would be of value to know how many times parathyroid hyperplasia or adenoma is found at post-mortem examination in cases which also have renal calculi. We have not had enough simultaneous neck examinations here to report our observations on this point.

Concerning the strictly urological features of this case, nephrectomy was necessary for the removal of a functionless, giant calculous pyonephrosis. The general improvement exhibited post-operatively was gratifying. However, when the destructive disease has not advanced to this degree, conservative therapy is indicated and has been emphasized (9).

Bacillus proteus, which was found in this case, is a particularly difficult organism to deal with in the urinary tract. In the first place, it splits urea, causing alkalinization favoring alkaline stone formation and, secondly, our chemotherapeutic efforts at its eradication have not been attended with much success. One may also stress the point that it is practically impossible to remove existent infection from a kidney which contains calculi.

In regard to the indicated subsequent treatment, the patient, on discharge from the hospital, had multiple calculi in the upper pole of a solitary kidney with probable B. proteus infection. Dietetic treatment of B. proteus urinary infection had been of no value in this clinic (9). Her best chances were apparently with operative measures. We proposed to explore the kidney and remove the calculi by pyelotomy or by pyelonephrotomy using operative x-ray control (10) to insure against leaving behind any residual calculi or fragments. If the anatomical configuration (blood supply) of the upper pole did not contra-indicate it, we intended to resect it. This would have permanently removed a probably deformed upper calyx which, if retained, would have tended to act as a persistent source of infection with its attendant likelihood of recurrent stone formation.

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EFFECT OF INFECTION ON CARBOHYDRATE TOLERANCE

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From time to time, patients are encountered who present the signs and symptoms of diabetes but whose subsequent course reveals their return to a normal carbohydrate metabolism.

The following two case histories illustrate examples of this temporary diabetic status.

CASE REPORTS

Case 1. History (Adm. 409323). S. W., a male, aged 44 years, was admitted to The Mount Sinai Hospital on January 18, 1937 with a history of tenderness and swelling on the back of his neck of six weeks' duration. His past history was irrelevant; there was no family history of diabetes. Two months prior to his admission to the hospital the patient became aware of polyuria and polydipsia. He had lost twenty pounds in weight during the previous year.

Examination. A large, indurated, tender swelling was present over the posterior triangle of the neck, extending into the intrascapular region. Deep fluctuation was noted. His temperature was 101.5°F. There was an odor of acetone on his breath.

Laboratory data. Urine: sugar, 5 per cent; acetone (nitroprusside reaction), 4 plus. Blood chemistry: sugar, 360 mg. per cent; urea nitrogen, 15 mg. per cent. The CO_2 combining power of the blood was 54 volumes per cent.

Course. The fluctuating swelling was incised and drained. A deep-seated burrowing infection was found on operation. The glycosuria was controlled with a diet containing 120 grams of carbohydrate, 60 grams of protein, and 60 grams of fat. Regular insulin was administered as follows: 30 units with breakfast, 20 units with lunch, 20 units with dinner, and 20 units at midnight. The fasting blood sugar on January 19 was 200 mg. per cent, and on February 5, 150 mg. per cent. The patient was discharged from the hospital on February 10 and referred to the Out-Patient Department for further observation and treatment. The patient was seen there repeatedly. The insulin requirements had been reduced to 15 units daily. On May 27 he returned to the clinic, complaining of increasing pain in the neck and head, with radiation to the left side of the occiput. There was limitation of motion of the head and neck in all directions. The diabetes remained well controlled with only the occasional appearance of a trace of sugar in the urine. Two days later the patient displayed resistance to passive movements of the neck, and complained of "electric shocks shooting" down into his legs. The tendon reflexes on the left side were diminished and a bilateral Babinski sign was obtained. There was an indefinite sensory level at about the seventh cervical segment. Within another day the patient complained of weakness in the left arm, was unable to walk, and began to experience difficulty in voiding. He was then admitted to the hospital, where a lumbar puncture revealed complete block. The cerebrospinal fluid contained 104 mg. per cent total protein and 13,500 white blood cells per cubic millimeter. A

pre-operative diagnosis of epidural granuloma was made. A high cervical laminectomy was performed (June 3, 1937) and a granuloma removed. During his stay at the hospital his urine was examined four times daily and no sugar was found. His diet had been increased to 200 grams of carbohydrate daily, 75 grams of protein, and 100 grams of fat. Fasting blood sugar was noted on three occasions to be respectively 130, 80, and 90 mg. per cent. The patient was transferred to the Veterans Hospital on October 8, 1937, where he remained for approximately one year. Because of the absence of glycosuria and because of the normal fasting blood sugars, a glucose tolerance test was done at the Veterans Hospital on October 21, 1937. The results were as follows: fasting blood sugar, 89 mg. per cent; one-half hour after the test dose, 111 mg. per cent; after one hour, 181 mg. per cent; after two hours, 200 mg. per cent. The urine remained sugar free.

The patient returned to the Diabetic Clinic of The Mount Sinai Hospital in November 1938. He was told to return to an unrestricted diet. A glucose tolerance test on November 8, 1938 showed the following: fasting blood sugar, 105 mg. per cent; one-half hour after the test dose, 140 mg. per cent; one hour later, 190 mg. per cent; two hours later, 155 mg. per cent; and after three hours, 90 mg. per cent. The patient has continued to have a normal fasting blood sugar level and repeated examinations of the urine have failed to show any glycosuria.

Case 2. History (Adm. 408823). L. K., a female, aged 48 years, was admitted to The Mount Sinai Hospital on May 9, 1936 with a history of pain and tenderness over the right scapula for six days. She had one diabetic sister. The patient's urine had been sugar-free until the onset of the recent illness.

Examination. Several furuncles of the breast and back were present and there was one extensive carbuncle over the right scapula. Glycosuria at the time of admission was marked.

Course. The carbuncle was incised and drained and the patient was referred to the Out-Patient Department where she was observed for the next six months. She was re-admitted to the hospital on November 11, 1936 because of the appearance of another carbuncle. The fasting blood sugar at that time was 160 mg. per cent. The urine remained sugar-free on a diet of 120 grams of carbohydrate, 60 grams of protein, and 80 grams of fat. The patient returned to the Out-Patient Department on November 16, 1936. Subsequently glycosuria reappeared simultaneously with a new crop of furuncles. She was hospitalized again (February 26, 1937). In the course of the elapsed seven months, the patient had lost almost 40 pounds. Two more crops of furuncles appeared, one of which again required hospitalization. At the hospital twenty units of insulin daily were required to control the glycosuria. The last furuncle was noted in October, 1937 and at the same time glycosuria reappeared for a brief period, after which time the patient's urine remained sugar free and the patient gained 11 pounds in weight. A glucose tolerance test on June 28, 1938 revealed the following: fasting blood sugar, 100 mg. per cent; one-half hour after the test dose, 145 mg. per cent; one hour later, 170 mg. per cent; two hours later, 100 mg. per cent; and three hours later, 85 mg. per cent—which may be considered as fairly normal values.

SUMMARY

In the two instances described, the patients presented an impairment of carbohydrate metabolism at the time of an acute infection. In case 2 there was evidence of recurrence of this phenomenon. The glucose tol-

erance tests in both patients returned to normal after recovery from the intercurrent infections.

It is well known that, in the true diabetic patient, the presence of an intercurrent infection will almost invariably increase the severity of the disease. It is, however, not so well known that these infections may impair the carbohydrate tolerance of certain apparently normal people to the extent of producing a temporary diabetic syndrome.

A CASE OF DIABETES INSIPIDUS OF INFLAMMATORY ORIGIN, TREATED WITH ROENTGEN RAYS

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The administration of extract of the posterior lobe of the pituitary usually furnishes adequate replacement of the missing antidiuretic factor in diabetes insipidus. The ultimate prognosis, however, depends upon the nature of the pathologic process responsible for the disturbed regulation of water exchange (16). Neoplastic, vascular, inflammatory and traumatic lesions of the hypothalamo-hypophyseal system, as elsewhere in the central nervous system, often produce irreversible damage. In certain instances, nevertheless, a direct therapeutic approach has brought about a termination of the syndrome. Tumors have been successfully removed with relief of polyuria while antiluetic measures have been of aid in lesions of syphilitic origin. The following case illustrates the beneficial effect of roentgen radiation in a case of diabetes insipidus following middle ear infection.

CASE REPORT

History (Adm. #426760). Miss F. M., a 22 year old white female bookkeeper, was admitted to the service of Dr. Israel S. Wechsler on July 10, 1938. She complained of increasing thirst for a period of five months and attacks of generalized involuntary trembling during the nine weeks before admission.

First admission. She had been well until 1937 when she began to have frontal headaches and post-nasal discharge. In December, 1937, after a febrile illness of twelve days, she had been admitted to the service of Dr. B. S. Oppenheimer with a diagnosis of acute otitis media and possible jugular bulb thrombosis. The only significant finding was a central perforation of the right ear drum which was discharging thick foul pus. On symptomatic therapy, her fever subsided and she was discharged, improved one week after admission.

Second admission. Shortly after, she developed severe occipital headache, chills, and fever. She was readmitted to the hospital, on Dr. Jacob Maybaum's service January 9, 1938, acutely ill and toxic; there was moderate nuchal rigidity; temperature was 105°F.; pulse, 122 beats per minute; respirations, 24 per minute. There was a blowing systolic murmur over the precordium. A right mastoidectomy was performed by Dr. Maybaum who found a drop of pus in the region of the mastoid tip. The right lateral sinus was obliterated and the internal jugular vein was ligated. Large doses of sulfanilamide were administered with development of optimum concentrations of the drug in the blood and urine. Her temperature continued to spike between 101°–106°F. for eight days following operation. A blood culture on the first postoperative day showed three colonies of beta hemolytic streptococci per cubic centimeter of blood. She developed bilateral papilledema and evidences of

meningeal reaction, but lumbar puncture was not performed. Two weeks after operation, her fever subsided and, except for papilledema of three diopters, there were no abnormal findings. Sulfanilamide was discontinued at this point. Five days later, however, the patient had a recurrence of severe headache with nuchal rigidity, bilateral Kernig sign, and temperature rise to 102°F. This exacerbation subsided without further sulfanilamide therapy. The patient was discharged five weeks after admission with a slight residual papilledema.

Interval History. Two months after her second admission, the patient began to have daily frontal headaches, often accompanied by nausea and vomiting. She drank large amounts of fluid, as much as 3 to 4 quarts of water daily, and urinated frequently day and night. In May 1938, she began to have attacks of generalized "trembling" similar to rigors, but without chilly sensations. These lasted for a few minutes and seemed related to the rapid consumption of cold liquids. During a period of six months prior to admission, she had not menstruated.

Third Admission. She entered The Mount Sinai Hospital for the third time on July 10, 1938.

Examination revealed a thin white female of 22, who appeared wan and tired. Both ear drums were retracted. The posterior portion of the right drum was replaced by granulation tissue. The lungs were clear. There was a soft blowing systolic murmur at the apex. The blood pressure was 110 systolic and 70 diastolic; pulse, 100 per minute. Mentally the patient was alert. There was slight anisocoria, the right pupil being larger than the left. The margins of the right optic disc were indistinct. There was slight hypesthesia of the right cornea. The deep reflexes were depressed and the abdominal reflexes could not be elicited. The left plantar response was not obtained, but there were no pathological signs. There was occasional inaccuracy on finger-to-nose tests with the left hand. These neurological signs were regarded as residual of an inflammatory process involving the meninges at the base of the brain, possibly an extension from the tip of the petrous bone. The history of polyuria and polydipsia pointed to the existence of a diabetes insipidus also of inflammatory origin.

Laboratory Findings. The hemoglobin was 90 per cent, white blood count, 8,000. The urine was acid; specific gravity, 1008, it was negative for sugar, albumin and formed elements. Urine concentration test showed a maximum specific gravity of 1010. Average specific gravity of daily routine urines was 1004. Phenolsulfonphthalein test showed 50 per cent excretion of the dye in two hours. The blood chemistry values were as follows: Blood urea 9 mg. per cent; sugar 70 mg. per cent; calcium 11.4 mg. per cent; phosphorus, 3.6 mg. per cent; sodium, 140 milli-equivalents per liter. Glucose tolerance curve was normal. Blood Wassermann test, negative. Spinal fluid study revealed normal dynamics, two mononuclear cells per cu. mm. Pandy test, negative; spinal fluid protein, 35 mg. per cent; sugar 55 mg. per cent; Wassermann, globulin, and colloidal gold reactions were negative. Basal metabolic rate was minus 16 per cent on admission; one week later it was minus 15 per cent. X-ray examination of the skull was normal.

Water Balance Studies. Careful study of the daily fluid exchange revealed a fluid intake which varied from 3 to 6 liters for twenty-four hours. The urine output was usually 1,000 cc. in excess of the intake for the same period. The maximum daily intake was 6,060 cc. and the maximum output, 8,200 cc. On the basis of her average weight (90 lbs.) the patient's urine output was approximately 120 cc. per kilogram per day. Fluid restriction was tolerated poorly and on several occasions fluid deprivation for twelve to fifteen hours could not be carried out because of intense thirst. On one occasion, during a urine concentration test, a moderate drop in urine output with an increase in maximum specific gravity from 1010 to 1014 was observed after the administration of three grains of Nembutal by mouth. Usual doses of as-

pirin, luminal and veronal had no demonstrable effect on water exchange. There was no alteration following lumbar puncture.

Course. During her nine weeks in the hospital the patient's temperature was normal except for a slight rise to 100.2°F. on three occasions. Several episodes of generalized coarse tremor were observed. These lasted several minutes and involved the trunk and extremities, with an accompanying spasm of the abdominal musculature. The rigor-like seizure was often followed by nausea. Several attacks were preceded by the drinking of large amounts of cold water. At no time were any psychic disturbances observed.

In view of the diabetes insipidus, pitressin (2 cc. subcutaneously) was given with a prompt reduction in urine volume from 6,200 to 2,500 cc. but with a slower and less marked effect on polydipsia. Following the administration of pitressin, the substitution of hypodermic injections of sterile water allowed a rapid return of water exchange to high levels. The urinary output rose in forty-eight hours after the administration of pitressin from 2,500 to 5,200 cc. with a slow rise in fluid intake. Readministration of pitressin (2.0 cc.) again curtailed urine volume for twenty-four hours, demonstrating a specific response. The urine specific gravity rose from 1010 to 1012.

Subsequent intra-nasal pituitary solution and dry pituitary powder by inhalation were given in an attempt to simplify replacement therapy. These preparations had a variable and less satisfactory effect on polyuria and polydipsia despite more frequent administration.

At the suggestion of Dr. Israel S. Wechsler, the patient was given a series of X-ray treatments to the pituitary region on the assumption that roentgen irradiation might bring about a resolution of inflammatory changes in the hypothalamo-hypophyseal system.

Irradiation was carried out in the general direction of the hypothalamo-hypophyseal region through right and left temporal fields, each measuring 6 by 8 cm. From August 23, 1938 to September 12th of the same year a total of 1,200 roentgens measured in air was delivered to each field. The following factors were used: kilovolts, 180; milliamperes, 6; filters 1 mm. copper, 3 mm. aluminum; focal skin distance 50 cm.; roentgens per minute 12.5.

During the first week of this therapy, pituitary solution nasally was continued. However, during the second week, it was discontinued and the urine volume remained between 3 to 3½ liters per day. The patient was discharged nine and a half weeks after admission, free of trembling spells. She had gained eight pounds in weight and was generally improved. Her urine volume was 3,700 cc. for twenty-four hours.

Observations of the patient two, three and seven months after discharge showed her to be active, with complete cessation of polyuria and polydipsia. Moreover, within a month after leaving the hospital, there was a return of normal menstruation. A concentration test seven months after discharge showed a specific gravity of 1022. Basal metabolism rate at this time was minus six per cent.

COMMENT

The clinical events preceding the onset of diabetes insipidus in this case suggest extension of the middle ear infection to the cranial venous sinuses and the meninges. The occurrence of the syndrome of diabetes insipidus as a sequel to inflammatory processes affecting the brain and meninges is not rare. Of 107 autopsy reports of diabetes insipidus collected by Fink (7), 13 per cent accompanied syphilitic basilar meningitis, 4 per cent were seen with tuberculous meningitis and tuberculomas of the

hypophyseal region, and 8 per cent were associated with non-specific inflammatory reactions in and about the hypothalamus. A review of the literature reveals cases occurring after the acute exanthemata, acute rheumatic fever, grippe, tonsilitis, sinusitis, as well as epidemic encephalitis (5, 9, 22). The volume of the urine was 120 cc. per kilogram of body weight, excreted by the patient, and is slightly below the average polyuria in cases of diabetes insipidus (8). There is, however, no correlation between the extent of the causal intracranial process and the severity or duration of the resultant diabetes insipidus. The course of the disease is usually a chronic one, although spontaneous arrests may occur and cures have been reported with such varied agents as lumbar puncture (3, 10, 12, 20), encephalography (17), and aminopyrine (13). In the case reported, neither lumbar puncture nor the administration of salicylates and phenobarbital had any effect on the water exchange. Nembutal, however, caused a drop in water output, a result which may be significant, in view of the known effect of the drug on hypothalamic functions (Ranson and Clark (14)).

In this case certain clinical features associated with the diabetes insipidus are of interest. The generalized involuntary muscular tremors which were observed resembled shivering movements and usually followed the ingestion of cold water. These were unaccompanied by any disturbance of consciousness and are to be differentiated from the convulsions of water intoxication described by Snell and Rowntree (18). Such rigor-like seizures are not uncommon in diabetes insipidus and may be a compensatory means of raising body temperature which is continually being lowered. Subnormal temperatures are frequently found in patients with diabetes insipidus and the substitution of warm water for cold is a means of combating heat loss and preventing "rigors" in these patients. Moderate variations in the basal metabolic rate are frequent. Rowntree (16) found a lowered basal rate in practically all his patients with secondary diabetes insipidus. In our case the basal metabolic rate was moderately depressed (minus 15 and minus 16) with a rise to minus 6 after the polyuria had disappeared. Also, symptoms suggestive of myxedema, such as coarseness of the skin, absence of sweating, and constipation, are not uncommonly found in diabetes insipidus.

Before considering the mechanism by which X-ray therapy may have affected the inflammatory intracranial process, the currently accepted views of the pathologic physiology of diabetes insipidus may be briefly summarized.

The fundamental defect in diabetes insipidus is the failure of the anti-diuretic factor of the *pars nervosa* of the hypophysis to exert its normal physiological control over water balance. Fisher, Ingram and Ranson (8) have shown that the secretion of anti-diuretic hormone is regulated by the supra-optico-hypophyseal system. In cats and monkeys, it was

found that the only lesions producing diabetes insipidus were those which destroyed the supra-optic nuclei on both sides of the body or interrupted the supra-optic-hypophyseal tracts. The latter resulted in atrophy of the supra-optic nuclei in the hypothalamus and in atrophy of the neural division of the hypophysis, including the infundibular stalk and median eminence. Biggart (1) demonstrated in human pathologic material discrete lesions of the supra-optic nuclei and supra-optico-hypophyseal tracts. The nucleus supra-opticus, situated in the anterior hypothalamus, is a well-circumscribed body of large cells straddling the optic chiasm on each side. The nucleus is superficial, reaching the surface of the brain in close relation to the pia mater. This makes it particularly liable to be involved by pathologic processes affecting the meninges in this region.

The evidence indicates that the anti-diuretic hormone acts mainly on the kidney and the polyuria is primary, while the polydipsia is secondary and compensatory.[1] Cushing and his co-workers (4) early found that diabetes insipidus in the dog did not develop after complete hypophysectomy. When a portion of the pars anterior was then transplanted, polyuria resulted. Von Hann (11) from a study of pathologic material and Richter (15), on physiologic grounds, concluded that the action of the anterior lobe is necessary for the production of diabetes insipidus. It is likely, therefore, that normal water balance is maintained by a synergism between the pars nervosa and pars anterior, although some rôle is played by other glands as well.

The beneficial effect of pituitary irradiation on the course of diabetes insipidus has been observed previously. Sosman (19) reported improvement in a case of diabetes insipidus due to xanthomatosis after deep x-ray therapy of the sella turcica. To our knowledge, x-ray therapy has been used chiefly in cases of this type in this country. However, Faelli (6) observed apparent cures by irradiation in two cases of diabetes insipidus of unknown cause and with marked polyuria. Vercelli (21) was able to terminate severe diabetes insipidus of five years' duration in a case of post-typhoidal meningo-encephalitis by a series of roentgen treatments to the diencephalon. Various explanations have been advanced to explain these results—the removal of xanthomatous tumor masses compromising the hypothalamo-hypophyseal system (Sosman), resolution of glial proliferation in inflammatory disease of the diencephalon (Faelli), and the possible stimulation of secreting structures to renewed activity (Vercelli). It is unlikely in the case herein described that irradiation caused cessation of the diabetes insipidus by depression of anterior lobe function, as there

[1] The possibility that the tuberal nuclei of the hypothalamus may be a central effector involved in the action of pituitrin has recently been suggested by Biggart who found damage to these nuclei in postmortem studies of 3 cases of diabetes insipidus unaffected by adequate doses of pituitrin during life (2).

was evidence of renewed glandular activity (that is, return of menses, restoration of the normal basal metabolic rate) following its use. The limitations of X-ray therapy are obviously great, since therapeutic success depends upon the potentialities of residual function of the *pars nervosa*. With degenerations of the supra-optic nuclei or complete destruction of the *pars nervosa* nothing can be accomplished. While this method may prove of value in cases of inflammatory involvement of the hypothalamic region, the results of X-ray therapy must be interpreted guardedly, since disappearance of the syndrome may occur spontaneously and sporadic cures have been attributed to a variety of therapeutic procedures.

SUMMARY

A case of diabetes insipidus, presumably of inflammatory origin, is reported as an example of the successful termination of the syndrome by deep roentgen therapy to the pituitary region.

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THE NATURE OF THE BLOOD IODINE

Preliminary Report

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For some time a series of studies has been made concerning the nature of the iodine that exists in the circulating blood. A considerable amount of data has been collected and a detailed report is planned at a later date. It was thought advantageous to submit this brief summary of part of the studies and to make the conclusions available to other workers before the complete report and the experimental protocols are published.

Aside from the technical difficulties encountered in the exact determination of the total amount of iodine present in mammalian blood—and these have been overcome—there exists the problem of interpreting the values obtained. The major problem has been the uncertainty of the biologic significance of the iodine present. Is all the blood iodine in an active hormonal form, or is part merely ingested iodine in transit? It is known that single doses of iodine taken by mouth raise the blood iodine level for days or weeks and because of this it has always been impossible to evaluate total iodine determinations in blood, especially when carried out on patients near the sea coast or in other iodine-rich areas.

To eliminate this error earlier attempts were made to separate "inorganic" iodine from "organic" or "hormonal" iodine by the use of differential solvents. For this purpose various alcohols or acetone have been most commonly used. The recent determinations by Treverrow (1) as well as these studies have shown that this supposed difference in solubility cannot be relied upon and is a variable determined by the solvent used, the ratio of solvent to blood, the duration of the reaction, and the temperature at which the extraction is carried out. Treverrow and Fashena showed, as confirmed by these studies, that all the iodine normally present in mammalian blood can be extracted by alcohol if the proper conditions are met. It is, therefore, apparent that too great significance cannot be attached to "organic" or "inorganic" iodine values when they are based on alcohol solubility or insolubility.

It was possible by a simple dialysis procedure, using running tap water, to cast some light on the nature of the blood iodine with the following results.

1. All the iodine normally present in the blood exists in a form which is non-dialysable through a cellophane membrane.

2. All the iodine which is added to blood *in vitro* or absorbed from the intestinal tract into the blood stream as iodide is completely dialysable from the blood in amounts up to at least four thousand times that normally occurring in the blood.

3. When the sodium salt of d-l-thyroxine is added to blood *in vitro*, from 40 to 60 per cent of this added iodine (in the form of thyroxine) becomes non-dialysable although the thyroxine in aqueous solution passes through the membrane readily.

4. The proportion of the added iodine in the form of thyroxine which becomes non-dialysable is, within limits, independent of the amount of thyroxine used or the amount of blood to which it is added.

5. Other colloids, such as gelatin, egg albumen and acacia render varying percentages of added thyroxine iodine non-dialysable. Iodides are freely dialysable from all these colloids.

6. Iodine in the form of diiodotyrosine, iodohippuric acid or tetraiodophenolphthalein is also rendered partly non-dialysable when added to blood *in vitro* or to the colloids studied but a smaller proportion of these compounds is fixed than of thyroxine as measured by the iodine remaining after dialysis.

7. The method of dialysis can be used as a practical method to determine the true level of "bound" iodine in the blood and to eliminate errors due to accidental contamination, therapeutic administration of iodides or previously undetected ingestion of iodine, resulting in much more constant "normal" values.

The experimental details and the protocols upon which these conclusions are based will appear in a subsequent report.

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SELECTED TOPICS IN TOXICOLOGY[1]

DEFENSE MECHANISMS OF THE ORGANISM AGAINST POISONS

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The short and cursory survey of the different ways, in which poisons can enter the body, and of the various modes of their administration brings us to the question of the defense mechanisms, by which the body is enabled to combat this menace. It is common knowledge that the organism can render harmless many poisons when taken in small amounts. Hence, every drug must be administered in a dose larger than the amount which can be destroyed or neutralized in the metabolic process. Otherwise no therapeutic or other effect can be achieved. This amount of the drug, which can be rendered ineffective by the body constitutes the *threshold value*. It varies with the different drugs and with different individuals and there is little doubt that the hormonal activity and the vitamin supply play an important rôle in the establishment of the body resistance to poisons. This is well exemplified by the loss of resistance to infections, and also to poisons in animal and man, caused by vitamin A deficiency. Mallanby showed that toxic products can be obtained from ergot, which cause subacute degeneration in the spinal cord in dogs and that these effects can be prevented by vitamin A. Moreover, it was shown that the paralytic form of ergotism occurs in populations whose vitamin A intake is probably deficient (1). While the normal organism is well equipped to counterbalance the effects of poisons, this is not the case in the presence of vitamin deficiency. Under these conditions, the body is unable to maintain the normal threshold value, below which toxic effects are not usually produced.

The great importance of this threshold value for the dosage of drugs and poisons is shown by the experience of Koeppe, an assistant of the famous pharmacologist, Schmiedeberg in Strassburg. Koeppe administered to himself 1 mg. of Digitoxin; as this dose proved quite ineffective, he later took twice this amount, namely 2 mg. The result was a grave intoxication and Koeppe became dangerously ill for a period of four days. The explanation of this unexpected highly toxic action lies in the following fact. The threshold value of Digitoxin for a healthy individual is

[1] This is the second in a series of lectures, delivered before The Mount Sinai Hospital staff during January and February, 1940. The first lecture appeared in Vol. VII No. 1, the third lecture will appear in the next issue of this Journal.

about 0.9 mg., a dose of 2 mg., therefore, is actually *more* than twice as large as the ineffective dose of 1 mg. The actual ratio between the effective amount of 1.0 mg. of Digitoxin to the highly toxic dose of 2.0 mg. of Digitoxin is best expressed in the following equation:

$$\frac{\text{dose of 1.0 mg.}}{\text{dose of 2.0 mg.}} = \frac{1.0 - 0.9}{2.0 - 0.9} = \frac{0.1}{1.1}$$

It is obvious, therefore, that the ratio is not 1 to 2, but 1 to 11. Koeppe had taken, therefore, the second time not twice as much as the first time, but *11 times as much*, a fact which explains the resultant violent toxic effect (2). Similarly, a dose of 0.02 gm. of morphine is not twice as large as a dose of 0.01 gm., but three times as large, for the threshold value for morphine is considered to be 0.005 gm. The effective value of 0.06 gm. of morphine, the *dosis letalis minima*, is, therefore, also not six times greater than that of 0.01 gm., but eleven times.

The ability of the body to destroy poisons is due to manyfold chemical processes, which can be performed by the cell and are effective normally, as the result of a large variety of fairly complex reactions. They are mostly of an organic catalytic nature, though other chemical mechanisms also play a rôle in the antipoison action of cells, as in the case of balancing osmotic pressure potentials and in maintaining hydrogen ion concentrations. These kinds of intermediary antipoison reactions may be grouped under the following headings: 1, Neutralization; 2, Oxidation; 3, Reduction and Hydrolysis; and 4, Synthesis.

1. Neutralization

This takes place automatically by virtue of the property of tissues and of blood to fix limited amounts of acid and alkaline valencies by their proteins, carbonates and phosphates, without causing any marked change in the hydrogen concentration of the medium. This *system of buffers* maintains partly the neutrality of the blood, while on the other hand, the blood neutrality is maintained by the renal excretion of the excess of fixed acids. The most common danger in disease and poisoning is the exhaustion of the alkaline reserve and the consequent greatly increased liability to the occurrence of acidosis. This occurs, for example, in cases of diabetes mellitus as *diabetic ketosis*. It can also be produced experimentally and for therapeutic purposes by administration of large quantities of calcium chloride or ammonium chloride.

The opposite effect, an increase in the alkaline reserve and the tendency to alkalosis can be the result of persistent vomiting, which causes loss of hydrochloric acid, or can be produced by the administration of large quantities of sodium bicarbonate. It is scarcely necessary to point out that the hydrochloric acid of the stomach plays an important rôle in the neutralization of alkaline poisons.

2. Oxidation

This is an important mechanism of decomposition of poisons and operates in various ways. I shall mention only a few examples: the decomposition of alcohol by oxidation into CO_2 and H_2O; the conversion by oxidation of the poisonous phosphorus into the innocuous phosphoric acid; the deamination of amino-acids; the breaking down of fatty acids by the Hofmeister-Knoop oxidation process, and finally the oxidative decomposition of the benzene-ring with the formation of muconic acid. I shall also mention the formation of phenol from derivatives of benzene, as in the case of the formation of the less toxic aminophenol from the extremely poisonous anilin; and finally, the oxidative transformation of benzoic acid into substituted benzenes as in toluol, xylol, benzyl-alcohol, etc. Of particular biological interest is the oxidative decomposition of various para-amine and phenylamine bases by aminoxydase, which is present in the liver and the intestines. This would suggest that it is concerned primarily with the detoxication of amines formed by bacterial action in the gut (Richter and Tingey (3)); again, amines such as isoamylamine and phenylethylamine (tyramine) are rapidly oxidized in the tissues. Adrenaline is not oxidized as rapidly as other amines and thus, it is doubtful whether the aminoxidase can be responsible for the rapid disappearance of adrenalin *in vivo*. According to Blaschko and Schlossmann (4), the cytochrome system in mammalian cells may participate in the destruction of adrenaline while substances such as *ascorbic acid* or *sulfhydryl compounds* may protect adrenaline from inactivation by the cytochrome system in a serious way *in vivo*; these substances protect adrenaline from inactivation by phenolases *in vivo*. It is possible that the prolonged action of adrenaline after the administration of ascorbic acid, as was observed by Clark and Raventos, can be explained by the specific inhibition of the cytochrome system, which caused a prolonged action of adrenaline.

Though the potency of poisons is generally reduced by the oxidative processes, the latter, however, may sometimes lead to the formation of even more toxic products than the original substance. For instance the oxidation of methyl-alcohol results in the formation of formaldehyde, which causes degeneration of the optic nerve fibers and blindness, being formed there in *statu nascendi*.

It should also be mentioned that though most of the oxidation processes take place through the action of oxygen, there exist in the animal body many oxidation reactions, in which a higher oxidation state is achieved by a reversible and temporary discharge of hydrogen ions; such oxidation-reduction processes without oxygen action are of great importance as catalytic reactions for the decomposition of poisons in the organism. They are brought about by numerous fermental agents (respirative ferment, cytochrome, phenoloxydase, peroxydase, cozymase, coferment,

etc.) but also by hormones and vitamins, as ascorbic acid, the aneurine (vitamin B_1), by glutathion, oxyaminoacids, and the fumaric and quinone systems. One of the *hydrogen acceptors*, used often in the decomposition of poisons, is methylene blue. It is transformed into the colorless leucomethylene blue by the action of hydrogen. A good example of a hydrogen donor in the cell, that is of a hydrogen transmitting group, is the nicotinic acid amid; it has enzymatic functions similar to those of adenylic acid in combination with a specific protein.

3. Reduction

The reduction and splitting processes cannot be considered as independent of oxidation, for both occur simultaneously in the animal body. They have a part in the transition of the pentavalent arsenous acid into the much more toxic trivalent arsenic acid, which is of great importance in toxicology. The organic arsenic compounds, of the form R − As = As − R are oxidized, however, according to Voegtlin and Smith, to the much more effective form of R − As = O. Further examples of such reductions are: the change from iodate to iodide, or the reduction of picric acid to picramic acid, which is excreted in the urine. One of the most disastrous effects of phosgen is probably caused by decomposition of this combat gas, after it has been absorbed by the cells, and by the formation of hydrochloric acid according to the formula: $COCl_2 + H_2O = 2\ HCl + CO_2$. A physiologically important splitting process, which results also in detoxication, is the almost instantaneous decomposition of the highly active acetylcholine into the one thousand times less active choline. This is accomplished by the splitting of the acetic acid group as the result of the activity of the choline esterase in the animal body. The acetylcholine content can thus be regulated by the increase or decrease of the choline esterase contents in the tissues. The choline esterase content is a determining factor for acetylcholine poisoning. The choline esterase can be inhibited artifically by substances such as physostigmine or prostigmine, thus, enhancing the acetylcholine effect. Other fermental decompositions and detoxications concern atropine, which is detoxified by an esterase in some herbivora (rabbits, goats); cocaine can be also decomposed by the body tissues. The fermental decomposition of the different digitalis glycosides, particularly that of strophanthine in the gastro-intestinal tract, is of great importance for their therapeutic use and toxic effects.

4. Synthesis

The great importance of this process, which takes place in intermediary metabolism may be emphasized by the following considerations.

A. *Glycuronic-acid synthesis* is, according to Lipschitz, a synthetic process of shorter carbon chains (3-carbon compounds) and not a product

generated by oxidation of carbohydrates, glycosides, maltosides or free glycuronic acid intermediated by alcohol. Slices of surviving liver of the rabbit, rat or guinea pig produce conjugated glycuronic acids; oxidation is an essential process in the production of glycuronic acids; an oxidation is catalyzed by heavy metal and is depressed completely by HCN and hypnotics. Oxygen cannot be replaced by methylene blue, fumarate or a combination of the two. Addition of dehydroxyacetone, pyruvic acid, lactic acid can increase the production of glycuronic acids in slices of liver by several hundred per cent *in vitro*. Slices of a fatty liver, caused by phosphorus degeneration, produce small amounts of glycuronic acids. The same is true of slices of liver from fasting guinea pigs. When injured by chloroform the fatty liver is highly active (W. L. Lipschitz (5)).

Alcohols, with the exception of methyl-alcohol and ethyl-alcohol, ketones and aldehydes, as for instance chloralhydrate and many aromatic and heterocyclic substances, are detoxified by means of glycuronic acid synthesis. The oldest known synthesis of this type is the glycuronic acid synthesis of camphor, described by Meyer and Schmiedeberg. To the same group belongs the detoxication of phenols, benzene, naphthol, thymol, borneol, menthol, morphine, many of their derivatives, and also phenylacetic acid (6).

B. *Sulfuric acid synthesis* and detoxication by esterization of the sulfuric acid takes place in the liver mainly with the aid of aromatic products of a hydroxyl group, as for instance with phenol, cresol, thymol, brenzkatechin, hydrochinone, resorcin, aminophenole, m and p oxybenzenic acid, etc.

$$C_6H_5 \cdot OH + H_2SO_4 = C_6H_5 \cdot O \cdot SO_2 \cdot OH + H_2O$$

Aromatic substances without the hydroxyl group, as for instance benzene, must be first hydroxylized, before combining them with sulfuric acid. The sulfuric acid esters are water soluble and they scarcely penetrate the body cells, unlike the toxic substances which are not combined with sulfuric acid.

C. *Glycocoll synthesis* concerns all the substances which are oxidized in the body into benzoic acid; they form hippuric acid with the liberation of water:

$$C_6H_5 \cdot COOH + H_2N \cdot CH_2 \cdot COOH = C_6H_5 \cdot CONH \cdot CH_3 \cdot COOH + H_2O.$$

Other acids, combining with glycocoll are salicylic acid, phenylacetic acid, anisic acid, etc. This reaction takes place mainly in the kidneys.

D. *Cholesterin*, by its direct addition to saponin, neutralizes the toxic and hemolytic properties of the latter.

E. *Sulfur synthesis.* The sulphydrate group (SH_2), which is derived from cystein, when added to poisons acts as a neutralizing agent. This principle is utilized in combating poisonings with cyanic acid and nitriles of the fatty group. Thus, in acetonitrile ($CH_3—CN$), malonnitrile

$(CH_2 \cdot (CN)_2)$ the addition of sulfur to the CN group produces an innocuous compound of the rhodan group (CNS). This is the detoxifying mechanism of the therapeutic intravenous administration of sodium thiosulfate ($Na_2S_2O_3$) in cases of poisoning with cyanic acid.

F. *Acetyl synthesis* also has a detoxifying effect, as for instance in the detoxication of anilin, when it is transformed into phenyl-amineacetic acid. Acetylation plays an important rôle in the pharmacology of sulfanilamide and its derivatives, as the acetyl compounds of sulfanilamide are insoluble and produce grave damage in the kidneys during excretion and cause the formation of calculi in the bladder.

G. Much less important is the detoxication synthesis by *methylation* which was recognized for the first time by Hofmeister in the excretion of *tellur* derivatives.

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CLINICAL PATHOLOGICAL CONFERENCES

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

Wednesday, March 15, 1939

Carcinoma of the Pancreas. Onset with Intestinal Indigestion and Glycosuria (9 months)

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

History (Adm. 434525; P.M. 11063). This was the first admission of a forty-three year old Italian, who complained of icterus, pruritus, asthenia and loss of weight. Before coming to this country in 1933, he had been employed on a small sheep farm. Since his arrival his occupation had been that of a paint-sprayer, the paint being known to contain lead and aluminum. His past history included an illness from the age of four to seven years, characterized by diarrhea, and termed "intestinal disease." For many years he had been experiencing occasional attacks of abdominal cramps which would be relieved by a milk and cracker diet for a day. In 1933 he came to The Mount Sinai Hospital Out-Patient Department because of attacks of abdominal colic and severe constipation, associated with marked gaseous eructations. Blood smear was examined for basophilic stippling, but none was found. He was then well until about one year before admission. Similar attacks then occurred and he began to have frequent, loose bowel movements, green to yellow in color. Although his appetite continued to be very good and he ate a great deal, he continued to lose weight. Polyuria became an additional symptom. Six months before admission he was told that he had glycosuria. A gastro-intestinal series done at that time was said to have been negative. He was placed on a diet, without insulin. Weight loss continued and weakness became progressively more marked. Three months before admission he again came to the Out-Patient Department. A fasting blood sugar was found to be 125 mg. per cent. He was placed on a high carbohydrate diet. His glycosuria was well-controlled on 20 units of protamine zinc insulin. He gained three pounds in weight. One month before admission icterus was noted; from that time on it had been progressively increasing in intensity. Pruritus, which was first noted one month before admission at the site of his insulin injections, had become generalized and more severe in character. His stools had been thin, malodorous, loose, yellow or gray in color, and associated with excessive flatulence. At times the stools had appeared foamy. His urine had been very dark in color, par-

ticularly in the four days before admission. Moderate polyuria was still present on admission. There had been no spontaneous abdominal pains in many months. In all, he had lost thirty-five pounds during the year preceding admission. He was referred to the hospital by the clinic.

Examination. The patient was emaciated, but appeared to be comfortable. The sclerae were icteric. A few small nodes were palpable along the left sternomastoid muscle. Heart and lungs were normal. The abdomen was distended but soft. The liver was palpable three inches below the costal margin; the edge was thin and regular. The splenic edge was readily palpable on inspiration. Prominent abdominal and flank veins were visible. Rectal examination was negative. Telangiectases were seen on the chest.

Laboratory data. Hemoglobin, 90 per cent; red blood cells, 4,750,000; white blood cells, 6,800 with a normal differential. Platelet count, 220,000. Sedimentation time, 1 hour, 5 minutes. Prothrombin time was 55 seconds. Urine analysis showed a specific gravity of 1.040, marked glycosuria, two plus bile, and urobilin of 1 to 4; microscopic examination was negative. Repeated urine analyses showed persistent choluria with urobilin positive in a dilution of only 1 to 2 or 1 to 4. Blood Wassermann test was negative. Blood chemistry showed a urea of 15; sugar, 170; cholesterol, 290; ester, 105; icterus index, 20; prompt positive Van den Bergh reaction; bilirubin, 4; Takata-Ara test, positive, 2 plus; total protein, 6.5; albumin, 4.6; globulin, 1.9. Echinococcus complement fixation test was negative in the hospital laboratory. However, the Board of Health laboratories reported a 4 plus echinococcus complement fixation test. A skin test for echinococcus was negative. A galactose tolerance test (after glucose fermentation) was within normal limits on two occasions. Repeated stool examinations showed formed contents, tan to brown in color, and only a faint trace of urobilin; the guaiac reaction was positive on most of the examinations. Fragility test on the red blood cells was normal. Attempted duodenal drainage was unsuccessful. Urine analysis for lead was negative. X-ray examination of the gallbladder region failed to reveal any radiopaque calculi. There was a suggestion of a globular subhepatic shadow in the right upper quadrant which was interpreted as a possible hydrops. A gastrointestinal series showed a normal duodenal bulb, and a constant narrowing of the second portion of the duodenum. Fluoroscopically, there was a suggestion of pressure by an extrinsic mass on the greater curvature of the antrum. Stasis, without constant obstruction, was present in the third portion of the duodenum. The roentgenologist interpreted these findings as indicating involvement of the second portion of the duodenum, with the possible presence of adhesions to the fourth portion, both probably a result of a lesion of the head of the pancreas. Electrocardiogram showed frequent ventricular extrasystoles.

Course. The diagnosis on admission was toxic cirrhosis. The patient was placed on a very high carbohydrate diet, with a daily intake of 500 grams of carbohydrate. On this diet, even though no insulin was administered, his glycosuria was usually only moderate and there never was any ketosis. Because of the laboratory findings of a high cholesterol and ester, marked bilirubinuria with only very small amounts of urine urobilin, the presence of only a faint trace of urobilin in the stool, the normal galactose tolerance tests, and the x-ray findings, it was decided to perform an exploratory laparotomy. The preoperative diagnosis was carcinoma of the head of the pancreas. At operation, the pancreas was found to consist of a stony-hard mass involving the head, body, and extending almost to the tail. A nodule was felt in the dome of the liver. The gall-bladder was markedly enlarged and filled with black bile. The veins in the gastro-hepatic and gastro-colic omenta were engorged, as found in portal obstruction. A cholecystogastrostomy was performed. Post-

operatively, he ran a febrile course, up to 102°F. daily. His icterus progressively increased. The icterus index rose to 56. Preterminally the index fell to 33. The cholesterol of the blood was 400 postoperatively. The urine contained bile but no urobilin at all. The stool contained only a faint trace of urobilin. A Levin tube drained contents which had no bile but gave a positive guaiac reaction. Fresh blood was present in the feces. The bloody stools continued and became more frequent. His prothrombin time was now 300 plus seconds. Bile salts and vitamin K were administered; his glycosuria was controlled with small amounts of insulin. His condition, however, became worse, went down-hill rapidly, and he died one week after the operation.

Necropsy findings. The *pancreas* was thickened and shortened. It was infiltrated throughout by carcinoma with complete obliteration of its normal lobulation. The carcinoma had invaded the proximal end of the duct of Wirsung, extending to the papilla of Vater which was filled with tumor tissue. The papilla was greatly thickened and protruded into the duodenum. The normal delimitation of the pancreas was absent, as a result of invasion of the surrounding fat tissue. Investigation of the cystic duct showed that at the point where it opened into the common duct, the latter was filled with neoplastic tissue, completely occluding the cystic duct. The common duct was involved throughout. The cystic duct was pale gray in color, whereas the hepatic ducts were deep green. The cholecystogastrostomy was intact; the stoma was patent. A tumor thrombus completely occluded the portal vein; this thrombus extended into the splenic vein. There were multiple metastatic implants in the *liver*. The tumor had also invaded and completely infiltrated the right adrenal gland. A huge, benign adenoma of the left adrenal gland was present.

Comment. Dr. Klemperer. The pathology may be correlated with the clinical findings. Although this man had a cholecystogastrostomy, his icterus was completely unrelieved because the flow of bile from the common duct to the cystic duct, to the gallbladder, and thence to the stomach, was completely impeded by obliteration of the normal communication of cystic and common ducts by the carcinoma. The pale gray color of this duct, with no trace of bile, may be cited as evidence of the inability of bile to reach the bile duct. The ascites and bloody diarrhea resulted from the portal vein thrombosis and subsequent venous stasis.

Dr. Baehr. The mode of onset is worthy of comment, i.e., the so-called "intestinal indigestion," as manifested by the frequent, loose, malodorous stools, yellow to gray in color, and associated with excessive flatulence. This results from the absence of the pancreatic juices from the small intestine. The occurrence of glycosuria in association with pancreatic malignancy should be noted. Glycosuria was present and could be directly attributed to the malignancy in fifteen per cent of the last one hundred cases observed at The Mount Sinai Hospital. The glycosuria is not due simply to a destruction of the islets, but in all probability represents a functional disturbance due to edema, obstruction of the duct, and similar processes. This is indicated by the fact that it is extremely variable and may clear up entirely during the course of the disease, so that normal sugar tolerance returns.

Wednesday, March 15, 1939

Hyperthyroidism (symptomatic) Precipitated by Diffuse Bone Metastases; Primary Tumor Undetermined During Life. Carcinoma (symptomless) of Lung

History. (Adm. 425907; P.M. 11020). The patient, a sixty-eight year old white, married female, was admitted to the hospital on July 21, 1938. Her past and family histories were irrelevant. Her present illness began six months prior to entry with a sore throat, accompanied by a slight chill. Shortly thereafter, there appeared pain in the left shoulder region, the right chest, and in the right hip. The right hip pain was associated with a sciatica nerve radiation of pain. An X-ray examination of the hip was negative. The probability of an infectious arthritis was suggested, and a sojourn to Florida was advised. While there, the patient developed anorexia, associated with a loss of weight of ten pounds. For a period of three weeks there was diarrhea. Occasional bouts of palpitation occurred. Even more striking was the persistence of the original complaints of left shoulder and right sciatic pains, completely unalleviated by the climatic change. She was unable to walk without pain and had become very apprehensive.

Examination. At this time (April, 1938), she consulted the referring physician, who found her to be pale and chronically ill-appearing. There were a few remaining infected teeth. The left arm appeared slightly atrophic. The heart sounds were of poor quality; the rate was 72 beats per minute, with many extrasystoles; the second aortic sound was accentuated. A soft systolic murmur was heard in the aortic area. The blood pressure was 174 systolic and 100 diastolic. A few inconstant râles were heard at both lung bases. No abdominal viscera were felt. Reflexes were normal. The bones were slightly tender.

Laboratory data. Fluoroscopy of the chest showed an enlarged left ventricle with a tortuous and uniformly dilated aorta. Urine: specific gravity, 1.018; faint trace of albumin and occasional hyaline cast. Sedimentation time was 38 minutes, with a rate of 29½ minutes in one hour. Hemoglobin, 72 per cent; red blood cells, 5,210,000; white blood cells, 7,800; platelets, 200,000; differential normal. Two stool examinations were guaiac negative. Blood chemistry showed urea of 19 mg. per cent; uric acid, 3.8 mg. per cent; sugar, 102 mg. per cent; calcium, 9.8 mg. per cent.

Course. Diagnoses were: 1. Osteo-arthritis with possible primary or secondary bone disease. 2. Arteriosclerosis and hypertension. 3. Infected teeth. 4. Malignancy to be ruled out, because of anorexia, pallor, and weight loss. Hospitalization was urged so that a more complete investigation might be carried out (Rehfuss test meal, gastro-intestinal series, and bone X-ray examinations). The patient, however, who was very high-strung and recalcitrant to all suggestion, refused. She went home and took sedatives for her "nerves" and iron for her anemia. Several days later, her physician found her to be fibrillating rapidly with a ventricular rate of 182, and a pulse rate of 106. Digitalization reduced the rate to 82 and abolished the pulse deficit. A repeat urine analysis again revealed a specific gravity of 1.018; microscopically many calcium oxalate crystals were seen. A repeat blood count showed a rise in hemoglobin to 82 per cent and a drop in red cells to 4,480,000. A consultant physician, impressed with the nervous state of the patient, suggested

the possibility of hyperthyroidism. A basal metabolism test was performed and was found to be plus 40 per cent. A consultant orthopedist agreed that the X-ray examinations of the hips taken at the onset of the illness were negative. A second basal metabolism test was reported as plus 110 per cent, but the patient was obviously uncooperative. She was given Lugol's solution, m V q.d., and admitted to The Mount Sinai Hospital. Here, her basal metabolism rate fell from plus 31 per cent on admission to plus 6 per cent. An electrocardiogram showed regular sinus rhythm, left ventricular preponderance, and absence of initial positive deflection in lead IV, suspicious of previous myocardial infarction. In view of her loss of weight, diarrhea, bouts of palpitation, her attack of paroxysmal fibrillation, elevated basal metabolism rate, and a lowering of her basal metabolic rate following the administration of Lugol's solution, a thyroidectomy was performed. The pathological report was hyperplastic thyroid in a colloid phase; there was a small calcified colloid adenoma. Following operation, the patient underwent a very definite change for the better. She became more pleasant and more cooperative. Occasional irregularity of the pulse was still noted. Because of the persistent complaint of left shoulder and right hip pain, X-ray examinations of these parts were taken to ascertain the cause of these symptoms. These were taken as soon as the patient had recovered sufficiently from the thyroidectomy to permit her to get to the X-ray department. They were reported as follows: Areas of rarefaction were seen in the innominate bone about the acetabular cavity, and involving the pubic bone. Examination of the left shoulder showed similar areas of rarefaction scattered throughout the head and upper portion of the shaft of the humerus. Part of the left lung and left ribs were visualized on the films taken of the left shoulder. This revealed a pathological fracture of the ninth rib; throughout the left lung there were innumerable small nodular infiltrations. These findings were interpreted by the roentgenologist as indicative of malignant bone and extensive pulmonary metastases. X-ray examination of the skull was negative for metastases.

Because of these findings further laboratory studies were performed as follows: Blood calcium was 10; phosphorus, 3.9; and phosphatase was 36 King-Armstrong units per 100 cc. (normal 5 to 8); urine was negative for Bence-Jones albumose. Routine urine examinations still showed no red cells, an occasional trace of albumin, and the occasional presence of calcium oxalate crystals. Although the X-ray findings pointed to a metastatic malignancy, the inability to demonstrate any primary lesion, i.e., there was no cough, no hematuria, no findings in the breasts, no headaches, no ovarian signs and careful section of the removed thyroid did not reveal any malignancy—the possibility of a primary bone disease of the multiple myeloma group was suggested. Therapeutically, a series of X-ray treatments were administered over the involved bone areas. One month following operation (July, 1938), while stepping from bed, the heel of her slipper broke. She complained of pain just below the left shoulder where she was steadied by the nurse. X-ray examination revealed that she had sustained a pathological fracture. Check-up X-ray examinations in September, 1938 showed practically no changes in the lungs or ribs. Some callus had formed around the pathological fracture in the left shoulder. In the pelvis, marked bone regeneration was seen in the right innominate bone, the head of the right femur, and both pubic bones. In November, 1938, the fracture of the left humerus had healed with considerable sclerosis. Further decalcification of the right innominate bone and of the eighth rib had taken place. The rest of the bones and lungs were essentially unchanged. The course was progressively down hill. Pain became more and more intense requiring large amounts of opiates. She died six months after admission to the hospital.

Necropsy findings. The *lungs* presented a picture of diffuse carcinomatosis of an unusual form. The pulmonary parenchyma was riddled with gray areas of infiltra-

tion. So widespread were they, that superficially they simulated a lobular pneumonia. The infiltrations, however, were fleshy to the touch. Microscopically, the tumor was an adenocarcinoma with distinct mucous cells. The *liver* did not contain any metastases. In sharp contrast to this, was the involvement of the skeletal structures. The *bones* were the site of a most extensive metastatic process. This was seen in all the bones examined (ribs, vertebrae, and pelves). The neoplastic cells had produced an osteosclerotic process, with spongy bone being replaced by condensed bone. This was most evident in the pelvis.

Comment. Dr. Bachr. Note the interesting sequence of events in this case, namely that the prolonged, intense pain and suffering resulting from the patient's malignancy, was a sufficient psychic trauma to initiate a true hyperthyroid state. That she actually had Graves' disease is indicated by the clinical picture and course, as well as the pathological picture of the removed thyroid.

Dr. Klemperer. This form of primary pulmonary carcinoma, with such extensive metastasis to bone is very rare. The origin of the neoplasm is probably from the mucous glands of the small bronchi. The small nests of malignant cells in the bones are comparable to a scirrhous carcinoma; the latter stimulates the production of connective tissue, while the former initiated striking new bone formation and ostosclerosis.

Reported by *Max Ellenberg, M.D.*

CLINICAL NEUROPATHOLOGICAL CONFERENCE

Monday, October 9, 1939

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

Case 1. Spongioneuroblastoma: With a Long Clinical Course and Repeated Surgical Intervention

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

History (Adm. 426506; P.M. 10993). A man, 42 years old, was admitted to the hospital in July, 1938 for the fourth time. His fatal illness began four years previously in August, 1934 with a sudden attack of dizziness, associated with turning of both eyes to the left and jerking movements of the head in the same direction. The episode lasted only a minute, during which time he retained consciousness but was unable to move his left arm. Similar episodes recurred on three other occasions at intervals of three and four months. One of them was marked by involvement of the entire left side of the body and was accompanied by nausea. Between these attacks he frequently felt dizzy. Near the end of the first year of his illness, he passed through an attack in which he lost consciousness for one hour and displayed clonic convulsive movements of his left arm and leg. The attack was followed by deep sleep. About this time he became aware of memory impairment, particularly for names, dates, and numbers; he also became very irritable.

Examination (first admission—May 1935). The patient was poorly developed and appeared to be poorly nourished. He was well-oriented and cooperative but somewhat depressed. There was bilateral hyposmia. The fundi were normal; a color defect in central vision was noted. The left pupil and the left palpebral fissure were larger than those on the right. There was a slight tremor of the tongue and of the outstretched hands. The deep reflexes were more active on the left than on the right side, with a questionable left Babinski sign and bilateral Chaddock signs. The abdominal reflexes were diminished on the left. Sensation was normal throughout. The blood pressure was 150 systolic and 80 diastolic.

Course. An encephalogram showed a questionable shift of the ventricles to the left; and a ventriculography which was carried out one week later showed even less convincing evidence of the shift to the left, but the right lateral ventricle was smaller than the left. It was felt that there was insufficient evidence to justify craniotomy and since the patient presented few disturbing symptoms, he was allowed to return home.

The second year of his illness was marked by eight convulsions, all accompanied by loss of consciousness. These were preceded by dimming of vision and a feeling of light-headedness. These prodromal symptoms occurred occasionally without being

followed by a convulsion. The patient now complained almost constantly of right parietal headache.

Examination (second admission.—May 1936). The findings were much the same as on the first admission, except that now there was early bilateral papilledema and the left side of the face was flattened. The right arm was held rather stiffly when the patient walked, while the left arm appeared to be weaker than the right; plantar flexion was absent on the left side.

Course. A second ventriculography was performed. It disclosed a dilated left ventricle which was displaced to the left; the right ventricle failed to fill with air. A craniotomy was then performed and a tumor composed of fleshy areas and cysts was enucleated from the right frontal and prefrontal areas. The tumor, after histopathological study, was reported to be a neurospongioblastoma. Radiotherapy was administered with apparently good results, although weakness in the left arm increased.

The patient left the hospital five weeks after the operation. Except for a slight thickness of speech, he continued relatively well, free from convulsive symptoms and gaining weight and strength for about a year. Then (at the end of the third year of his illness) convulsive attacks recurred, accompanied now by unconsciousness. Following one of these attacks he experienced severe pain in the lower spine and found that he could not move his legs.

Examination (third admission—October 1937). Paraparesis with tenderness over the sacral spine and residual pyramidal tract signs on the left side were found on examination. There were no sensory disturbances.

Laboratory data. Roentgenology: X-ray examination of the spine disclosed a compression fracture of the fourth lumbar vertebra. (The fracture had probably occurred during the patient's last convulsive seizure.) Cerebrospinal fluid: initial pressure, 86 mm. of water; dynamics, normal; cells, 35 red blood cells and 34 lymphocytes per cu. mm.; Pandy, 2 plus.

Course. After six weeks in the hospital the patient was transferred to another institution where he remained for seven months and then returned home. Two months later he was readmitted to The Mount Sinai Hospital because of the increasing frequency of generalized convulsions, persistent weakness of the left arm and leg, and severe frontal headaches.

Examination (fourth admission—July 1938). The patient was alert, well-oriented, and cooperative. The corneal reflexes were diminished on both sides; the left pupil was slightly larger than the right and there was blurring of both discs with a left central facial paralysis. The tongue deviated somewhat to the right. The deep reflexes in the upper extremities were hyperactive; Chaddock, Oppenheim, and left Babinski signs were present. The left arm was held flexed at the elbow but could be moved voluntarily.

Laboratory data. Cerebrospinal fluid: initial pressure, 190 mm. of water; final pressure (when 12 cc. of fluid had been removed), 100 mm. of water; cells, 66 per cu. mm., of which 6 were mononuclears; sugar, 45 mg. per cent: total protein, 212 mg. per cent; Pandy, 4 plus.

Course. Ten days after admission a second right frontal craniotomy was performed. Tumor tissue was found to be infiltrating the surrounding brain tissue; consequently as much tissue as possible was removed from the right premotor area. As the brain was very edematous, the bone flap could not be restored. The cerebrospinal fluid pressure increased and shortly after the operation the brain herniated through the operative site. Finally clear fluid under pressure appeared, discharging from the wound. The patient began to have occasional bouts of fever. During the next two months he became progressively more and more apathetic and incontinence set in. Following an attempt to excise the herniated brain tissue, the

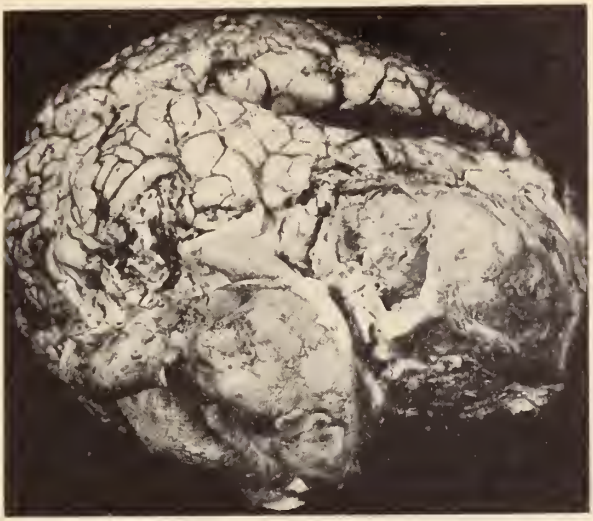

FIG. 1 (case 1). A photograph of the surface of the right cerebral hemisphere showing the extent of the herniation of brain and tumor tissue.

FIG. 2 (case 1). Coronal sections of the brain showing the tumor tissue and a cyst in the mesial half of the right temporal lobe, the upward compression and narrowing of the thalamus, and the herniated mass of brain and tumor tissue in the right fronto-parietal region. The left lateral ventricle and the third ventricle are displaced in the direction of the herniation.

patient developed a left hemiplegia and hemi-analgesia, a coarse irregular tremor on the right side, and a left homonymous hemianopsia. Repeated spinal and cisternal punctures were done and sulfanilamide was administered. The herniation of brain tissue increased and the patient's general condition declined gradually, with death ensuing five months after his last admission.

Necropsy findings. Projecting from the right fronto-temporal surface of the brain there was a soft fluctuating mass of herniated tissue (fig. 1). It was composed of yellowish fluid and gelatinous brain substance and included brain tissue from the lateral surfaces of the frontal and temporal lobes and part of the parietal lobe.

The ventral surface of the right temporal lobe, the right internal carotid artery, and the ventral surface of the right cerebellar hemisphere were covered by a film of gray fatty substance. The meninges over the left hemisphere were clear and glistening; the brain itself felt firmer than usual.

On sectioning the brain, a well-demarcated tumor was found occupying the right hemisphere (fig. 2), extending from just inside the frontal pole to the junction of the parietal and occipital lobes. In the extreme frontal region it was more dorsal in location, occupying almost the entire width of the hemisphere near the dorsal surface and measuring about $6\frac{1}{2}$ cm. in width and $3\frac{1}{2}$ cm. in depth. Posteriorly it merged with a mass of more or less disorganized and fibrotic tissue having a grayish-pink coloration and an island of yellowish tissue at the center. It was smooth, glistening, and quite resistant to pressure. In one area posteriorly, it was highly vascularized. In the mesial and inferior portions of the occipital lobe, it was less clearly demarcated, presenting a granular surface with pink discoloration. In the inferior and lateral portion of this area there was a small cyst filled with grayish gelatinous material. Protruding from the hippocampal sulcus was a small herniation of tumor tissue; another small tumor mass occupied the lower edge of the island of Reil in the left hemisphere. Posteriorly, underlying the corpus callosum on the right and overlying the quadrigeminate plate, there was another herniated mass. The ventricular system, compressed in its dorsoventral plane and spread out laterally, was displaced in the direction of the lesion. Peculiarly enough, the left lateral as well as the third ventricle was dislodged in the direction of the lesion, probably a result of the herniation.

Microscopic. Sections of the tumor stained with hematoxylin and eosin showed tumor cells which in some places were very numerous and compact and in others rather sparse. In crowded areas, they tended to be arranged in strands about blood vessels and to lie among dense bundles of collagenous fibers, assuming a mosaic pattern (fig. 3 A). Elsewhere they were distributed throughout a reticular network. The nuclei were of varying sizes, but chiefly of two types: either large, pale, and vesicular and located in cells with elongated cytoplasmic processes; or small, rounded, and hyperchromatic and located in cells with scanty cytoplasm. Many mitotic figures and occasional giant cells were seen. The tissue was highly vascular and many of the vessel walls were thickened. Small extravasations of blood were encountered throughout the tissue, often about small blood vessels. Brownish granular pigment occurred near some of the vessels, evidence of previous extravasations.

In Bielschowsky preparations there were large ovoid cells containing dark cytoplasm and a slight round nucleus. Some of these cells gave off one or more long spiral processes, which bifurcated at varying distances from the cell body (fig. 3 B). Some of these cells were unusually large and gave off very long, irregular processes.

Nissl stains showed dense infiltrations of small round dark-staining nuclei about blood vessels. Occasionally a larger nucleus containing coarser basophilic granules

would be seen among the small round nuclei. Nissl stains also showed large irregular cells with round vesicular nuclei and very pale, pink cytoplasm and, rarely, a binucleated cell.

Comment. Dr. Globus. Of particular significance in this case are the Jacksonian convulsive seizures which marked the beginning of the fatal illness and punctuated the entire clinical course. Such an onset

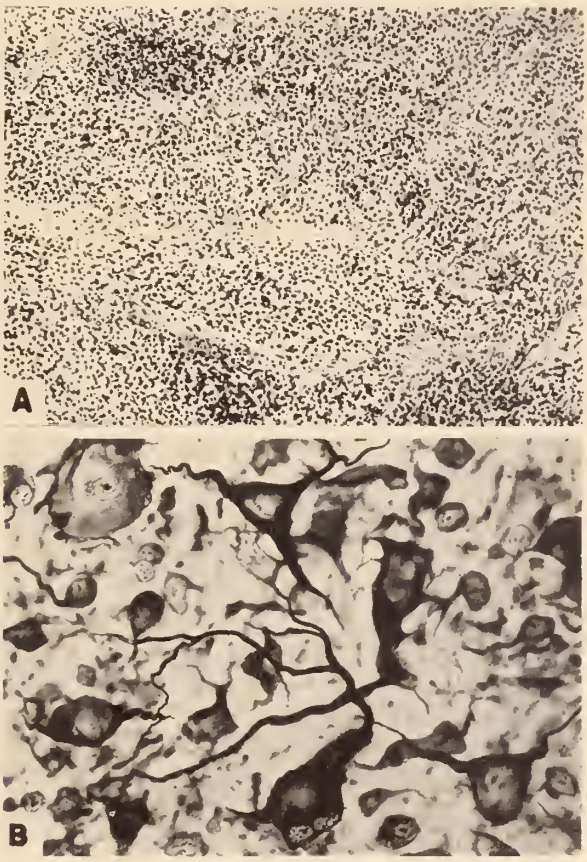

FIG. 3 (case 1). A. A section of tumor tissue demonstrating the tendency of the tumor cells to form a mosaic pattern and to be arranged in small groups. Several giant cells are present (Nissl, 120×).

B. Abnormal cell forms occurring in the tumor tissue. (Several cells have been retouched to eliminate blurring due to variations in their optical levels.) (Bielschowsky, 800×).

is not uncommon for such, for instances in which tumor resides in either the temporal or frontal lobe, but it is most frequently met with in cases of brain tumor of the glioneuromatous or spongio-neuroblastic varieties. It is not improbable that the neuronal elements, in various stages of ripening, present in these tumors act as trigger zones provoking fragments of cortical discharges, which spread, often to assume the char-

acter of an outspoken Jacksonian convulsive seizure. Thus, it would seem that the tumor cells of the neuronal variety may on occasion function, but in a disordered fashion.

Another feature in this case is the almost negative encephalogram in the early clinical stage. This is quite common in the infiltrative form of tumor such as glioneuroma or spongioneuroblastoma.

Repeated studies of the histological character of this tumor, as material was made available with each surgical revision, revealed the progressive and accelerated tendency for greater malignancy of this growth. This has already been noted in a previous study[1] showing that the neuroectodermal tumors, when subjected to some alterations in their environment, have a tendency to acquire a more rapidly growing and histologically less differentiated character.

Reported by *B. H. Schaffner, M.D.*

[1] Globus, J. H.: Die Umwandlung gutartiger Gliome in bösartige Spongioblastome. Ztschr. f. d. ges. Neurol. und Psych., 134: 326, 1931.

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.

Insensible Perspiration in Children. IV. The Influence of Salt. G. J. Ginandes and A. Topper. Am. J. Dis. Child. 55: 1176, June 1938.

An attempt was made to determine the effect of single doses of salt on the insensible perspiration of "hospital normal" children. A definite decrease in the rate of insensible loss of weight was effected in all cases.

This decrease can most logically be explained by an increased osmotic pressure of the blood with a resultant decrease in vapor pressure of fluids available for vaporization. The theory that the salt effect is primarily due to retention of fluids is less tenable. The possibility that the effect is augmented by a direct depressant action of salt on the secretory activity of sweat glands cannot be gainsaid.

Whatever the mechanism, the fact that there was no change in the total heat production confirms the conception that insensible perspiration is a function not only of heat regulation but also of the state of tissue hydration.

Multiple Peripheral Neuropathy versus Multiple Neuritis. I. S. Wechsler, J. A. M. A. 110: 1910, June 4, 1938.

After giving a historical review of the subject the author points out that from a pathological and etiological point of view the term multiple neuritis, as denoting inflammation, is a misnomer in most cases. Actually the changes are degenerative rather than inflammatory. So, too, the "neuritides," hitherto regarded solely as the result of alcoholism, diabetes, pregnancy, cachexia, etc., have been shown to be the result of vitamin privation. The author therefore suggests the substitution of multiple peripheral neuropathy or polyneuropathy for multiple neuritis and the reservation of the last term only for those cases in which inflammation actually occurs. The change in terminology would thus conform with the concepts of encephalopathy as opposed to encephalitis and myelopathy as opposed to myelitis.

Urinary Cholesterol In Cancer. E. Bloch and H. Sobotka. J. Biol. Chem. 124: 567–572, July 1938.

Two thousand liters of urine from the wards of the New York City Cancer Institute were obtained through the courtesy of Dr. S. S. Goldwater, Commissioner of Hospitals. The extraction of these urines showed that they contain about ten times as much cholesterol as urine from normal controls. Cachectic patients with other diseases, such as tuberculosis and heart disease, show normal cholesterol values, whereas hypercholesteroluria is known to occur in kidney disease and perhaps during pregnancy.

Two possible causes for the appearance of cholesterol in urine in cancer are discussed. That of destruction of tumor tissue, rich in cholesterol, is given preference.

Origin of Carcinoma in Chronic Gastric Ulcer. S. H. Klein. Arch. Surg. 37: 155, July 1938.

The term "ulcer-carcinoma" of the stomach is defined as a carcinoma which has developed in a primary benign chronic peptic ulcer. The author critically reviews and discusses the clinical and pathological criteria for the diagnosis of ulcer-carcinoma. Only pathological examination may be used as a basis for diagnosis. It is proved that there is no one pathologic finding which may be considered pathognomonic of the pre-existence of a chronic benign peptic ulcer. Further, it is demonstrated that the characteristic pathologic features of chronic benign peptic ulcer may be exhibited in every detail by primary gastric carcinoma which has undergone peptic ulceration.

The author's serial block method for the complete anatomic study of gastric ulceration is described.

In a series of 141 cases of chronic gastric ulcer and 353 cases of gastric carcinoma there were but 2 cases in which the diagnosis of ulcer-carcinoma could be suggested on the basis of the strictest pathologic criteria. Although they are most severe and conservative, these criteria are nevertheless still open to criticism. It is therefore concluded that malignant degeneration of chronic gastric ulcer, if it occurs at all, is rare. In view of the rarity of proved ulcer-carcinoma, there is insufficient justification for early radical surgical treatment of gastric ulcer based only on the possible danger of malignant degeneration.

A Modification of the Incision for Thoracoplasty. Howard Lilienthal. Ann Surg. 108: 154, July 1938.

The author's modification consists in making a Maurer's incision for the upper stage of the thoracoplasty, and a second incision upon the ninth rib and parallel with it, but not connecting with the first incision. Through this, by suitable retraction, the 8th, 9th, and 10th ribs may be resected. If it is desirable to resect the 11th or even the 12th, the incision may be made along the upper border of the 10th rib; when with suitable retraction the other ribs may be resected.

The principle is that two short incisions are better than one long one, following a well-known rule of surgery.

Built-Up Films of Steroid Compounds. H. Sobotka and E. Bloch. J. Biol. Chem. 124: 559, July 1938.

Continuing the researches begun in collaboration with Dr. Langmuir on the investigations of built-up monomolecular films of biologically important organic substances, the authors studied the behavior of various bile acids and related steroid compounds in monomolecular layers. Cholanic acid and, to a certain extent, lithocholic acid form monomolecular layers which can be built up on slides.

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CONTENTS

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.

Changes of address must be received at least two weeks prior to the date of issue, and should be addressed to the Journal of The Mount Sinai Hospital, Mt. Royal and Guilford Avenues, Baltimore, Maryland, or 1 East 100th Street, New York City.

VITAMIN A: THE DISTRIBUTION OF VITAMIN A IN THE BODY[1]

HANS POPPER, M.D.

(From the Cook County Graduate School of Medicine and the Cook County Hospital, Chicago)

If we know the chemistry of a biologically active substance we are interested in its localization in the organism, since this gives an important clue as to its role in the body. Vitamin A is distributed throughout the human and animal body and is now chemically defined as a long alcohol chain and identified by chemical analysis and biological assay. As a fat-soluble vitamin, it is extracted from the organs in the lipoid fraction. The chemical assay is based upon this method of extraction. The vitamin A concentrates used therapeutically originate from such a non-saponifiable lipoid fraction. Thus it would seem that there is a close connection between vitamin A and the body lipoids.

The study of vitamin A deficiency, however, gives a different impression as to the site of the effect of this vitamin and its role in the organism. Vitamin A deficiency is characterized as an affection of the epithelium. The histological picture reveals the following phenomena in most of the tissues, according to Wolbach (1): An atrophy of the involved epithelium is followed by a reparative proliferation of the basal cell layer. The newly formed product differentiates into a stratified, keratinizing epithelium independent of the original structure and its function. The newly formed epithelium in the different locations is always similar to the epidermis. In glands and their ducts, the proliferated keratinized cells may finally fill the lumen. Cysts filled with yellow, cheesy masses appear and the glands undergo atrophy. This process is sometimes mistaken for abscess formation. On the other hand, the metaplastic dry epithelium serves as a *locus minoris resistentiae* for infections. The whole process may be summarized as a disturbance in the specific differentiated growth of epithelium with undifferentiated proliferation.

The typical eye changes, xerophthalmia and keratomalacia, are due to such a metaplasia of epithelium. They appear very late. One of the earliest manifestations occurs in the skin (toad-skin). Follicular papules, due to hyperkeratosis of the hair follicles and atrophy of the sweat and sebaceous glands, develop. The affection was observed among adults in

[1] Lecture delivered April 25, 1940 at the Blumenthal Auditorium of The Mount Sinai Hospital as part of the Symposion on Vitamins.

different countries. Recently Lehman and Rapaport (2) reported its occurrence in children of poor families in this country. The growth of the teeth is altered early due to epithelial changes of the enamel-forming organ. The enamel formation stops and the dentin formation decreases, both leading to deformities of the teeth. Unspecific growth of the epithelium continues, epithelial islands are formed surrounded by bizarre ossification and calcification of the mesenchyma. Tumor formation, odontomas, may follow (3). The dental changes occur in human beings and animals, in the latter so early and so typical that Schour, Smith and Hoffman (4) based a biological assay for vitamin A on the disturbances of the dentin formation. The respiratory epithelium reveals similar alterations. Plugging of the bronchioli occurs and may be the cause of the pneumonia found in hypovitaminotic children. Alterations of the mucous membrane of the gastro-intestinal tract are reported with achylia and enteritis. Greater interest was aroused when changes of the epithelium of the urinary tract were noted. There is no doubt that urinary calculi may develop in vitamin A deficiency, but up to the present time there is not sufficient evidence that lithiasis in the human is the consequence of vitamin A deficiency or is influenced by vitamin A therapy.

All this leads to the conclusion that vitamin A is related to the histodifferentiation of epithelium; its absence induces mere proliferative growth. There is, however, one phenomenon in vitamin A deficiency which is not primarily related to disturbed histodifferentiation, namely disturbances of vision (night blindness): the regeneration of the visual purple after its bleaching (Wald's cycle, (5)) is disturbed; the dark adaptation is impaired. Night blindness is one of the first signs of avitaminosis. The examination for dark adaptation is the most widely used clinical test for vitamin A deficiency at the present time.

How does the influence of vitamin A on histodifferentiation of the epithelium and its connection with the vision purple agree with the fact that it is always chemically demonstrable in association with lipoids and most often in organs not altered by vitamin A deficiency? Are these organs, such as the liver or the fat depots, just storage places, and is the active vitamin present in small amounts in the epithelium? The extensive chemical analyses by Moore (6) and others have shown that in the organs sensitive to hypovitaminosis minute amounts of vitamin A may be found. Whether these small quantities are located at the site of their effect—the epithelium—can only be decided by an established histological demonstration of vitamin A.

In the last eight months we have tried to perfect by means of fluorescence microscopy an histological method for the visualization of vitamin A. From the results thus far obtained we feel that the method is already established, though the time available was not sufficient to investigate thoroughly all its possibilities. Previously similar experiments on differ-

ent oils as well as on human and animal tissues were made by von Querner (7). He described fluorescent paraplasmatic inclusions in the epithelial cells of the liver, the adrenal cortex and the pituitary gland, which faded upon irradiation. He maintained that the same fluorescence could be found in vitamin A concentrates and expressed the belief that this fluorescence of the tissue constituents was due to the presence of vitamin A.

Vitamin A itself has a characteristic green fluorescence in ultra-violet light which is rather quickly destroyed by irradiation with the ultra-violet light. This fading—called by Peacock "delumination" (8)—runs parallel with a destruction of the biological activity and a disappearance of the characteristic color reactions of vitamin A. This green fluorescence is used in the fluorescence microscopic demonstration of vitamin A.

Fluorescence microscopy uses as its light source a light rich in ultra-violet rays; all visible light is cut out by a filter system. One observes the tissues in ultra-violet light by means of an ordinary microscope. Fluorescent material present in the tissue sections changes the ultra-violet light to some form of visible light. Above the tissue section there are two types of light (fig. 1): 1) the visible light produced by fluorescence and 2) the remaining ultra-violet light. This ultra-violet light is finally cut out by a brown filter over the eye piece which permits passage of the visible light. The principle, therefore, is the use of two filters, one determining the original light and the other cutting out this light, while only the newly formed fluorescent light is observed. Light other than ultra-violet light can be used as primary light and the future may see the development of fluorescence microscopy with visible light.

By the use of a filter system (9) dealing with ultra-violet light of relatively long wave-length, many fluorescent tissue constituents are visible. Even in unstained sections a good orientation is possible. The study of all these fluorescent details is a promising field in histology. By proper preparation and fixation many substances, not otherwise visible may be seen. Staining with fluorescent dyes (fluorochromy (9)) or fluorescence produced by the coupling with different reagents may make visible many other substances. The chief difficulty, however, is not the visualization of substances made possible by fluorescence microscopy, but their fixation in the tissues.

These difficulties caused us to turn from the study of proteins, which first attracted our interest, to the examination of the easily fixed fats. Here we came across a startling phenomenon. If one studies frozen sections of tissues, fixed in formalin for only a short time, one is impressed by a striking fluorescence, present especially in the liver. This fluorescence disappears within half a minute while the section is under observation. In sections mounted in mineral oil which is the usual mounting medium in fluorescence microscopy, the fluorescence is not visible, due to

the solution of the fluorescent substance in mineral oil; nor is it visible after too long fixation. Treatment of the section with lipoid solvents extinguishes the fluorescence.

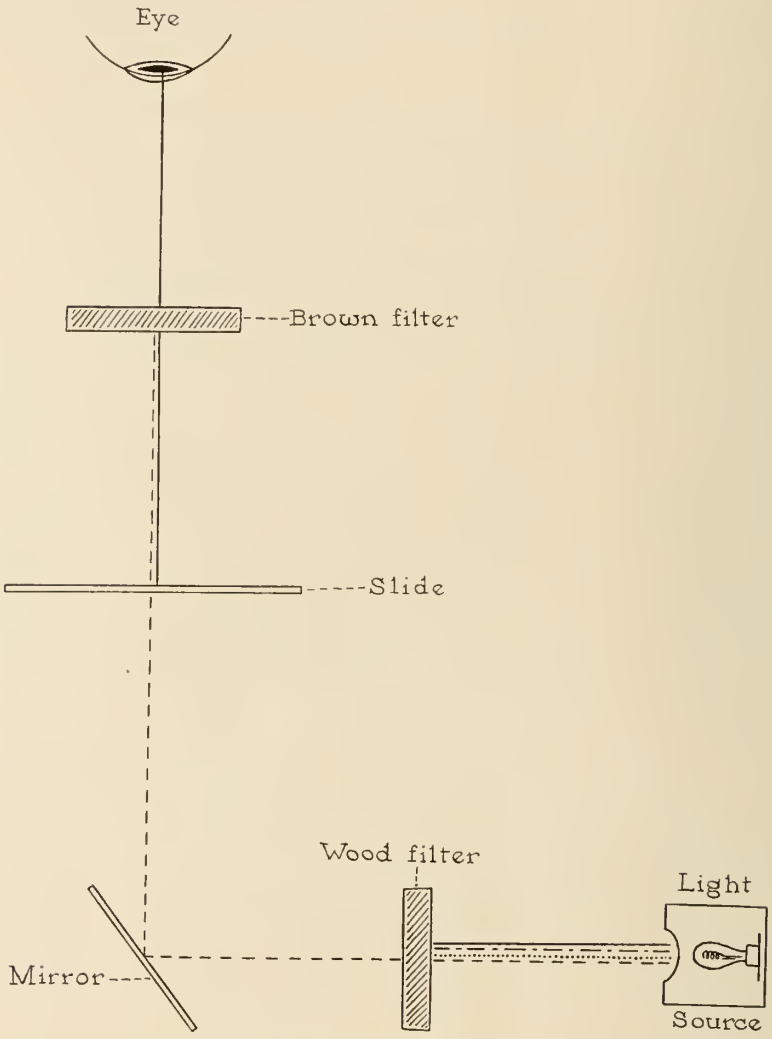
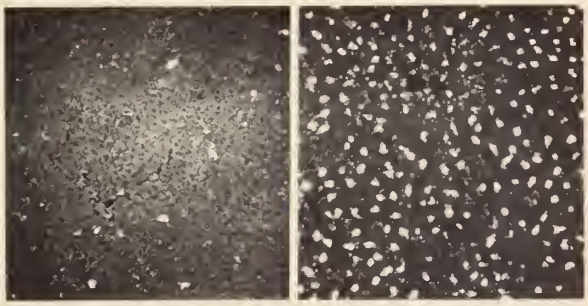


Fig. 1. Principle of the fluorescence microscope. Schematic drawing

When we tried to find the lipoid responsible for this characteristic fluorescence, we found the same behaviour in vitamin A concentrates. In thin aqueous emulsions of vitamin A concentrates a similar striking green fluorescence of the droplets was visible under the microscope. It faded within one minute and only a dim blue fluorescence remained. We, therefore, assumed that this characteristic fluorescence in the tissues might

be due to the presence of vitamin A. The same assumption had been made previously by von Querner.

The following evidence is now available for this assumption (10): 1) There is a similarity between the fluorescence of vitamin A concentrates and of the tissue constituents in the human and animal body. 2) The distribution of the characteristic fluorescence in the body agrees with the distribution of vitamin A, as one may conclude from chemical analysis or biological assay. 3) Histochemical analysis yields the same reactions in the droplets of the vitamin concentrates and in the fluorescent tissue constituents: they have the same solubility; they are unchanged by alkali, acids, and reducing agents; they are destroyed by oxidizing agents. The stability in reducing agents differentiates this fluorescence from a similar fluorescence of vitamin B_2, which is quickly destroyed by reduction. 4) The best evidence is offered by experiments on avitaminotic and hyper-



a b

FIG. 2. Fluorescence photomicrographs of rats' livers.
(a) Normal rat. Vitamin A in epithelial and Kupffer cells.
(b) Hypervitaminotic rat. The Kupffer cells are loaded with vitamin A; the epithelial cells contain high amounts.

vitaminotic animals. All our studies on experimental animals were performed in association with R. Greenberg from the Department of Physiology, Northwestern University Medical School (11).

In the liver of the normal rat rather high amounts of the characteristic fading fluorescence are present in the Kupffer and epithelial cells (fig. 2a). The liver of the vitamin A-deficient rat does not show this fluorescence. Only a dim blue fluorescence of the cytoplasm is visible, as in normal livers after fading of the vitamin fluorescence or prolonged fixation.

If such a vitamin A-deficient rat is fed with vitamin A, the typical fluorescence reappears. The amount depends on the dose of vitamin A given. The chemical analysis for vitamin A agrees with the amount of the fluorescence. To date we have not found another substance besides vitamin A or carotene which produces the characteristic fading fluorescence in the organs of vitamin A-deficient rats. None of the different fat bodies

or other vitamins causes reappearance of the fluorescence. In rats with other vitamin deficiencies the vitamin A fluorescence is not changed if care is taken in the administration of vitamin A.

The livers of hypervitaminotic rats are extremely rich in this fluorescence. The fading takes more than a minute. The epithelial cells contain much vitamin A, but even more is found in the Kupffer cells. The latter are apparently increased in number and loaded with vitamin A (fig. 2b).

The localization of vitamin A is determined by staining with fluorescent dyes. With the latter method lipoids can be demonstrated more distinctly and more completely by fluorescence microscopy than with the usual fat stains in visible light. Phosphine 3 R produces a silver-white fluorescence of the lipoids and visualizes more lipoids than sudan 3. If the section is treated with acetone, the silver-white fluorescence cannot be produced; this indicates the specifity of the reaction for lipoids. With methylene blue some fats acquire a white fluorescence but less fat bodies are visualized than with phosphine 3 R. The fading green fluorescence of vitamin A surpasses the fat fluorescence and thus vitamin-carrying fats are differentiated from others. Besides that, the methylene blue stained section can be observed in visible light if the ultra-violet filter is changed to a ground glass filter. This facilitates the localization of the fluorescence. Such studies have revealed that the carrier substances of vitamin A are lipoids, which with few exceptions are demonstrable by the above stains. We see, therefore, that the fluorescent tissue constituents are not vitamin A *per se*, but rather the vitamin A-carrying lipoids. Hence one can designate vitamin A as a vital stain for some lipoids.

The adrenals of avitaminotic rats show no green fading fluorescence. In normal rats, and in deficient ones after repletion, vitamin A is present in the fascicular layer of the cortex. In hypervitaminotic rats much more fluorescence is seen. The medullar and glomerular layers are free of the fluorescence, although the latter contains the same amount of lipoids as the fascicular layer. Thus, a non-specific solution of vitamin A in the available lipoids can be excluded and a specific affinity for certain lipoids assumed. In the kidney vitamin A is found in the interstitium of the cortex, apparently in the capillary endothelium. The distribution follows the nephrons and is not uniform. In hypervitaminosis more is found and even the tubular epithelium shows vitamin A. In the lung it is found in the septa and in hypervitaminosis in the alveolar cells as well. In the lung and renal cortex the vitamin is not bound to demonstrable lipoids. The interstitial cells of the ovary are rich in the fluorescence. All these organs are free of the fluorescence in vitamin A deficiency.

In the intestine usually no vitamin A is found. After oral administration it may be seen in the lumen and within the wall of the duodenum and upper jejunum. It can be traced through the epithelium of the villi into their stroma. The vitamin is then collected in the lacteals which show it

throughout the entire wall. Figure 3 shows the lymphatic resorption of vitamin A.

The retina of the rat contains a considerable quantity of vitamin A in fine droplets. This does not disappear entirely in avitaminosis; the amount only seems to be reduced. In animals which are grouped for vitamin A assay, according to the United States Pharmacopeia method XI (revised 1937), the other organs are free of vitamin A within twenty days, long before the first signs of hypovitaminosis appear. The retina, however, contains considerable amounts after fifty days. We found vitamin A present there even in rats dying of avitaminosis with ulceration of the cornea.

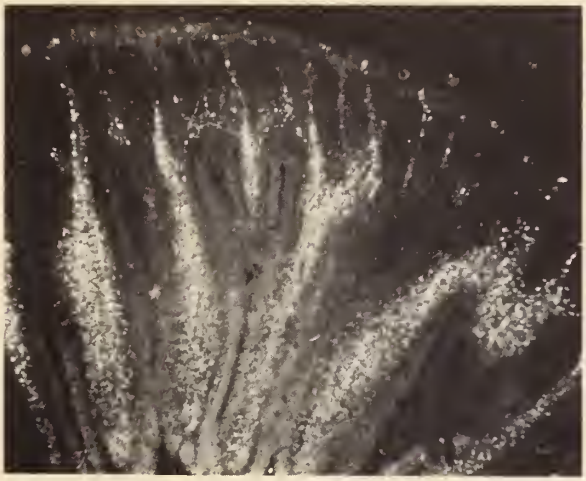


FIG. 3. Fluorescence photomicrograph of rats intestine after oral intake of vitamin A. Resorption of vitamin A: presence in the epithelial cells and the stroma of the villi and in the lacteals.

This review of the histological distribution of vitamin A in rats offers at the same time a strong support for the histological method. Recently a similar method was used by German investigators (12, 13). Another proof was yielded by studies on fish which R. Greenberg carried out with me (14). The epithelial cells of the common marine fish, such as halibut or seabass, are loaded with vitamin A, present in the many fat droplets. In fresh water fish, like pike or perch, almost no green fluorescence is present, despite the same amount of lipoids, but a dimmer brown-red fluorescence appears which fades much more slowly. Spectroscopic analysis of the organs of fresh water fish has shown instead of vitamin A, with an absorption maximum at 328 millimicrons, another substance with a maximum at 350 millimicrons (15). This substance, called vitamin A_2, has biological activity (16). We prepared liver oils from fresh water fish which revealed a brown-red slowly fading fluorescence instead of the green fluorescence of

the common liver oils originating from salt water fish. The liver oil fed to vitamin A-deficient rats caused a red fluorescence of the liver cells instead of the usual green fluorescence. Vitamins A_1 and A_2 can, therefore, be differentiated by fluorescence microscopy.

Physiological studies aided by the histological method confirm many results of the investigations on vitamin A with chemical analysis performed by Moore and others. The depletion takes a much longer time in adult rats than in growing ones; even after several months vitamin A is found in the organs of the adult rats. The younger animals have much smaller depots. At birth only traces are found in the liver. The endothelial cells of the liver and kidneys are the last cells in the parenchymatous organs to lose the vitamin. The retina never loses it completely.

If the vitamin A depots of deficient rats are restored by oral administration of vitamin A, the fluorescence appears first in the intestines and then in the Kupffer cells of the liver. After five hours liver cells, adrenal, lung, and kidney reveal it. Last of all, the fluorescence of the ovary and fat tissue reappears. Subcutaneous or intramuscular administration of the same vitamin dose requires more time. The better resorption in the intestine and the esterification of the vitamin in the intestinal mucosa are probably responsible for this difference. Vitamin A is stored in the liver chiefly in form of the ester (17).

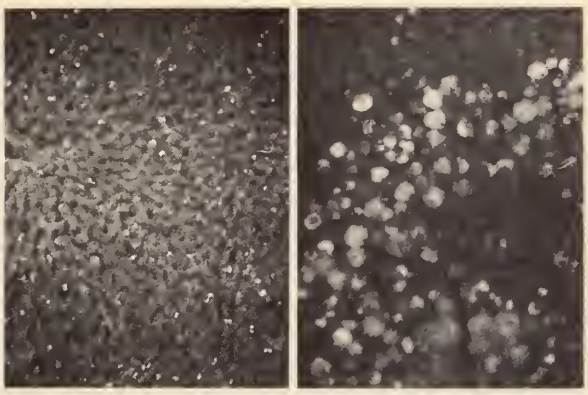
Carotene, as provitamin A, is changed in the body to vitamin A. The site of this splitting is not definitely established. Carotene has a dimmer green fluorescence than vitamin A and is easily differentiated from it under the fluorescence microscope. With carotene, relatively higher amounts and a longer time is required in order to obtain a storage comparable to that of vitamin A. The fluorescence first appears in the endothelial cells of liver, lung and kidney. Later on, the other storage places of vitamin A show the fluorescence. The intestine is usually free of the fluorescence after administration of carotene. This leads to the assumption that carotene is split in the endothelial cells of the mentioned organs,especially in the Kupffer cells of the liver (Drummond, 18).

In the course of the first four weeks of the depletion, the restoration after oral administration is regular. After this time the first signs of hypovitaminosis appear in the growing animal and the intestinal resorption suffers. Feeding of vitamin A or carotene leads to irregular results, a fact which impairs many methods of biological assay. We are trying to employ the histological method in order to derive a simple biological assay. Vitamin A disappears from the liver of growing animals within a depletion period of twenty days. In such animals as show no signs of avitaminosis and intact intestinal resorption the characteristic fluorescence in the liver is looked for after feeding the substance in question.

The distribution of vitamin A in human organs can be studied with the same method. In the human liver it may be found in different locations

(fig. 4a). The Kupffer cells almost always show it since they almost regularly contain lipoids (19). Very seldom are these fats free of vitamin A. In the liver cells vitamin A may be seen in fat droplets; then again it is visible in small lipoid droplets which would not be demonstrable by the common fat stains. These droplets either fill the liver cells irregularly or line the edge of the cells like pearls on a string. The "wear and tear" pigment, or lipofuscin, is often loaded with vitamin A. After fading of the vitamin fluorescence the proper brown fluorescence of the pigment is visible. Small amounts of vitamin A may be diffusely spread over the cytoplasm of the liver cells, not bound to demonstrable lipoids.

There is a great variety in the amount and distribution of vitamin A in the human liver, even under normal conditions. In this connection our findings by fluorescence microscopy agree with results attained by chemical



a b

FIG. 4. Fluorescence photomicrographs of human livers.
(a) Vitamin A in Kupffer cells and in fine lipoid droplets in epithelial cells.
(b) Local fatty infiltration. Vitamin A in the fat droplets in the liver cells.

analysis (Moore (20), Wolff (21), and others). We found less instances in malnutrition e.g. in carcinoma of the esophagus. But in adults without liver damage some vitamin was always demonstrable. Very little storage was found in newborn and young infants. The embryo of about five months has considerable amounts of vitamin A in the liver. Toward the term these depots are reduced and at birth only traces are seen. It takes several years until the normal depots of the adult are reached.

The fat droplets in the liver cells show usually much fluorescence, e.g. in local fatty infiltration (fig. 4b). In fatty livers without liver damage, as in obesity, the fat droplets are fairly fluorescent.

In sepsis, infectious diseases, uremia or in other conditions with toxic hepatic edema, the Kupffer cells are rich in vitamin A whereas the epithelial liver cells are free. Normally the Kupffer and adjacent epithelial

cells have a similar vitamin content. In local liver damage, as in a Zahn infarct with thrombosis of the branches of the portal veins, the infarct is free of vitamin A, while the surrounding tissue shows an excess of the vitamin. With the common histological technique in visible light such infarcts are sometimes hardly differentiated from the normal tissue.

In generalized liver damage the vitamin A storage is reduced. In pathological fatty livers, as in alcoholics, the fat droplets are poor in green fluorescence. In acute hepatitis and liver atrophy, only traces of vitamin A are found, usually in an irregular form in the Kupffer cells. In compensated cirrhosis small amounts are seen, chiefly in the fat droplets; in decompensated cirrhosis with superimposed acute hepatitis, the liver is nearly free of vitamin A. Complete absence is noted in luetic hepatitis of children.

The evaluation of the pictures in human livers is very difficult, and further study on larger material will be required. Up to now a few points are obvious which may serve to clarify the irregularity of the chemical results. A quantity of vitamin A as determined by chemical analysis has not always the same significance and may not contradict different histological pictures. For instance, fat droplets retain vitamin A much longer than other sites of localization. The vitamin found there is probably less available for use.

The absence of vitamin A from the liver cells in liver damage may be due to an inability to take it from the Kupffer cells. The picture in hepatic edema suggests this possibility. An inability to hold vitamin A may also be responsible (22). An increased use of the vitamin in the organism in liver damage is revealed by its decrease in the other body depots. The intestinal resorption of vitamin A is reduced in jaundice (23). That can only be significant in chronic liver damage. The depletion in acute hepatitis occurs before the resorption impairment can be of influence. Vitamin A deficiency in liver damage was clinically known—hemeralopia is seen in some cases of cirrhosis—and was recently supported by adaptometry (24). All this suggests vitamin A therapy in liver diseases, although there is no evidence that improvement of the liver condition itself will result from this therapy.

The determination of the dark adaptation by various methods as an alleged test for vitamin A deficiency gave widespread results in apparently normal persons (25, 26). Some investigators, therefore, assumed slight hypovitaminosis in a certain percentage of the population. Dietary surveys support this opinion when the intake is compared with the requirements (27, 28). The widespread results of these studies would agree with the variety of the distribution in the liver. As we never found complete absence in normal livers, one must assume that hypovitaminosis may occur with still existing liver depots or that not all the vitamin in the depots is available for immediate use. An early marked reduction of the depots may therefore be significant. The low amount in the livers of children

suggests the tendency to hypovitaminosis and indicates the usefulness of vitamin A therapy. The same holds true for cases of malnutrition, liver damage, nephritis or infectious diseases.

The reduced vitamin storage in the liver in infectious diseases agrees with chemical analyses (29, 30). It brings to the foreground the role of the Kupffer cells. They are the transfer stations in vitamin A metabolism, as the experiments on rats have shown. They are first filled in restoration of deficient rats, they are last emptied in depletion and probably split carotene. The role of the Kupffer cells in fat metabolism is manifested by many experiments (Jaffé and Berman, 31). One assumes that the Kupffer cells after blockade are unable to store vitamin A (32, 33). In infectious diseases, however, as well as in uremia or diabetes, the Kupffer cells are not free of vitamin A. They are filled and the liver cells are empty.

FIG. 5. Fluorescence photomicrograph of human adrenal. Vitamin A in the glomerular and fascicular layer of the cortex.

That suggests a block for transmission of vitamin A from the Kupffer cells to the liver cells. In fever the vitamin A level of the blood is low (34), but the blood carotene level is considered to be relatively higher (35). This was explained by the inability to split carotene. Brazer and Curtis (36) found similar disturbances in diabetes combined with hypovitaminosis as determined by biophotometry. These results may now be explained with the mentioned block for transmission. Only in severe liver damage are the Kupffer cells also free of vitamin.

In the human adrenal much vitamin A may be seen in the fascicular and glomerular layer as well (fig. 5). The distribution runs usually parallel with that of the double refractile bodies. A great variety is present, as in the liver. Focal or uniform exhaustion occurs in infectious diseases or liver damage. There is a complete reconstruction of the adrenal in the first years of postnatal life. The vitamin A distribution participates in

these changes. Up to the second month, however, no vitamin is seen, despite the presence of lipoids in the adrenal.

Vitamin A appears in the tubular and Leydig cells of the testicles. In the latter a brown fluorescing pigment is visible after fading of the vitamin fluorescence. Vitamin A and the brown pigment appear after puberty and disappear in higher age and in exhausting diseases. This indicates a relation to the sexual functions.

In the mature ovary vitamin A is found in fine lipoid droplets in the subcapsular connective tissue, irrespective of the menstrual cycle. It is visible in the corpus luteum. In the granulosa cells it is present in rather fine droplets which do not give double refraction; in the theca lutein cells there are larger, less fluorescent droplets over a brown fluorescent pigment, together with double refraction. After the dissolution of the corpus luteum these theca lutein cells are scattered over the stroma. They finally lose their vitamin A and disappear entirely in the climacterium. The relation of vitamin A to the sexual functions is further demonstrated by its presence in the luteinized lining of cysts.

The inactive breast tissue contains no vitamin A; the lactating glands are rich in vitamin-carrying droplets.

The normal human kidney is free of vitamin A in contrast to the rats' kidney. In nephritis and nephrosclerosis it is found in lipoid droplets in the tubular epithelium and in the interstitium, sometimes combined with double refractile bodies. Not all lipoids of the kidney carry vitamin A. The recent theories of nephrosis of Bell and Volhard claim that the lipoid storage in nephrosis is caused by a pathological permeability of the glomerular loops. The lipoids passed are reabsorbed and deposited in the tubules. Vitamin A apparently passes the same way. It was found in the urine only where somewhat damaged kidneys existed (37, 38). In contrast to other vitamins, the presence of vitamin A in the urine is not a sign of saturation of the body, but of a pathological permeability of the glomeruli. The appearance in the urine seems to be a more sensitive test than that of the double refractile lipoids.

The fat cells in fat tissue and those scattered in different organs contain small amounts of vitamin A. The distribution in the different fat depots of the body varies. The smaller the fat droplets are, the stronger their fluorescence. Degenerative fatty changes, as in fat necrosis, are always free of vitamin A. As in the liver, its presence may differentiate a normal fat storage from a pathological fatty degeneration.

The tissues not mentioned are free of the vitamin. The brain does not contain any. The epithelium of skin, cornea, bronchi, urinary tract, and enameloblastic organ is also free; the gastro-intestinal tract, except during resorption, is free. Positive chemical results in some of these organs are caused by its presence in the adjacent fat cells, e.g. in the submucosa.

The influence of vitamin A on histodifferentiation and the increased proliferation in deficiency gives rise to the question of its presence in

tumors. In investigations with A. B. Ragins (39), it was shown that only those tumors contain vitamin A which originate from a vitamin A-carrying mother tissue. Nothing was found in most of the sarcomas or carcinomas, even when fat was present. Vitamin A was found in some hepatocellular carcinomas, in some breast tumors, and in solid ovarian tumors, as in xanthofibroma, dysgerminoma or granulosa cell tumor. Its distribution in the ovarian tumors offers some clue as to the original mother tissue in the ovary. Cortical adenomas of the adrenal are very rich in vitamin A, even when the adrenal contained little.

In so-called hypernephroid carcinomas, vitamin A was found in most structures except the desmoplastic ones. Even the papillary features which are considered to be a proof for the renal origin of the hypernephroma may contain much vitamin A. Tubular adenomas of the kidney are free despite the presence of much fat and doubly refractile bodies. If we consider that the adrenal and the adrenal adenomas are rich in vitamin A and the normal kidney is free, then we have to admit that the fluorescence microscopic examination supports the original hypothesis of Grawitz as to the adrenal origin of the hypernephroid carcinoma.

Thus, the presence of vitamin A neither prevents nor aids in tumor formation. Its local presence does not influence proliferative growth.

At the present time a few conclusions may be drawn from the histological examination as to the role of vitamin A. At the site of the first morphological signs of hypovitaminosis (the epithelium) no vitamin A is demonstrable under normal conditions. As to the influence of vitamin A on histodifferentiation, we have to assume a distant effect without local presence or with the presence of only minute amounts.

Actual presence, however, is required for other functions of vitamin A. For its action in vision high amounts are locally necessary and it does not completely disappear even in extreme deficiency. The presence of vitamin A in the cells concerned with the production of the sexual hormones indicates a role in sexual functions.

The different localizations of vitamin A in the normal organism may be conditioned by one of the following factors: 1) actual participation in biological processes (probably on chemical reactions, such as in the retina), 2) distribution, such as in the Kupffer cells of the liver, 3) storage such as in the fat tissue, and 4) secretion such as in the lactating breast. The presence in the liver cells may be related to several of the above factors.

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EXUDATIVE TUBERCULOSIS CONFINED TO A LOWER LOBE AND SIMULATING LOBAR PNEUMONIA

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When a pulmonary lobar consolidation is confined to a lower lobe, it is almost invariably assumed to be caused by the pneumococcus, while a possible tuberculous etiology is usually overlooked. The following case of exudative tuberculosis, simulating pneumococcus pneumonia of a lower lobe, is described in order to call attention to the need for differentiating these two conditions from the point of view of prognosis and treatment. Furthermore, this case demonstrates the possibility of early clinical recognition of the tuberculous nature of a lower lobe pneumonia.

CASE REPORT

History: (Adm. 439765) The patient, H. A., was a married woman, aged 27, who was seen at home on April 30, 1939. She stated that except for recurrent migraine headaches she had been in good health until three weeks before admission. At that time she suffered a mild, presumably afebrile, upper respiratory infection, the chief symptom of which was a cough with little mucoid expectoration. The day before she was seen, her cough had become intensified and she experienced malaise and a feeling of warmth. She took her temperature for the first time and found it to be 104°F. by rectum. She then summoned a physician, who made a diagnosis of lobar pneumonia and requested her to try to collect sputum for pneumococcus typing before commencing specific therapy.

When I examined the patient on the same day, I was impressed by her general appearance of well-being. She sat up in bed and related her story without any visible discomfort. She coughed occasionally without expectoration but she did not appear febrile, nor did she reveal any respiratory distress or tachypnea. She had received no coal tar medication nor other analgesics or opiates which might cause a drop in temperature and improvement in subjective comfort. It was thought that she was suffering from an upper respiratory infection with tracheitis and that the diagnosis of lobar pneumonia was a tentative one which had proved to be erroneous. However, her temperature was 104.5°F. by rectum.

Examination revealed no abnormalities in the nose, pharynx, tonsils, ears or cervical lymph nodes which might point to an upper respiratory infection with complications. However, there was a distinct diminution in the respiratory excursions of the left side of the chest. There was dullness on percussion over the lower half of the left chest posteriorly, below the level of the fifth dorsal vertebral spine. Over most of this area there were bronchovesicular breath sounds. But in a localized region below the angle of the scapula, the breath sounds were definitely tubular. Over the latter site bronchophony and whispered pectoriloquy could be elicited. There were numerous râles of the crepitant and subcrepitant varieties. The remainder of the examination revealed no further abnormalities.

The diagnosis was apparently lobar pneumonia, but there were many atypical features which cast doubt upon the correctness of this impression, despite the localization of the lesion to a lower lobe. Among these features were the unusual onset, the apparent well-being of the patient despite her high fever, the absence of respiratory symptoms, and the presence of extensive pulmonary signs including subcrepitant râles in what purported to be a lobar pneumonia of twenty-four to thirty-six hours duration. A tentative diagnosis of tuberculous pneumonia of the left lower lobe was made and the patient was questioned again for possible previous evidences of pulmonary tuberculosis. She recalled that a year earlier, after a respiratory infection lasting three weeks, she had coughed up blood-streaked sputum on two occasions. Her physician had examined her fluoroscopically and had made a diagnosis of pleurisy, but had not examined her sputum. After a few days in bed she had felt well again and had forgotten the incident. This additional history confirmed the diagnosis, and because of unfavorable home environment for management of her acute illness she was referred to the hospital.

The patient was admitted to the hospital the next morning, May 1, 1939. The history obtained and the findings on examination were essentially the same as those presented above.

The clinical diagnosis was lobar pneumonia of the left lower lobe. Because of the localization to a lower lobe, the provisional diagnosis of a tuberculous etiology was not accepted and the patient was treated as a case of pneumococcus pneumonia. A type 20 pneumococcus was obtained from the sputum after inoculation into a mouse. Sulfapyridine was administered *per os* beginning with 2 grams and followed by 1 gram every three hours until a total of 24 grams was given. Then an additional 15 grams were administered in doses of 1 gram every four hours.

Laboratory Data: On admission, a blood count showed the hemoglobin to be 88 per cent, white blood cells 10,900 per cu. mm., staff cells 54 per cent, polymorphonuclear neutrophiles 21 per cent, lymphocytes 25 per cent, monocytes 7 per cent, basophiles 1 per cent. The urine contained a faint trace of albumen and occasional leucocytes. The blood urea nitrogen was 12 mg. per 100 cc. and the blood sugar 115. A blood Wassermann test and a blood culture were negative.

A roentgenogram of the chest showed a pneumonic infiltration of the left lower lobe (fig. 1). There was no evidence of cavitation.

Course: Despite sulfapyridine therapy the patient's cough and fever persisted. Her temperature during the first week spiked between 99.6° and 103°F. and during the next week it frequently reached 104° and 105°F. Her pulse was relatively slow compared to her temperature, ranging usually between 90 and 100 beats per minute. There was a progressive increase in the expectoration of thick green sputum.

During the first four days the sputum was not examined for tubercle bacilli since the patient was considered to be suffering from the usual form of pneumococcus lobar pneumonia. At the end of this time, however, several observations suggested the possibility of pulmonary tuberculosis. A von Pirquet test was strongly positive. The spiking fever curve, the absence of tachypnea, the slight leucocytosis and the failure to respond to sulfapyridine were all unusual for a pneumococcus pneumonia. On May 5th, the first examination of the sputum with acid-fast stain revealed numerous tubercle bacilli. Tubercle bacilli were also found in three additional specimens of sputum taken on successive days. Pneumothorax therapy was begun on May 9th and the patient was given refills of 200 to 300 cc. on five occasions in the next eight days. A roentgenogram of the chest taken on May 15th revealed a left pneumothorax with 50 per cent collapse of the left lung. This film confirmed the localization of the pneumonic lesion to the left lower lobe.

On May 17th the patient was transferred to Bellevue Hospital where she received pneumothorax therapy twice a week for six weeks. On July 15th she was transferred

to Seaview Hospital. Shortly after her arrival at Seaview Hospital her temperature fell to normal and has remained normal ever since. She continued to receive pneumothorax therapy twice a week at Seaview Hospital until the left lung was 95 per cent collapsed. She left Seaview Hospital November 11, 1939. However, almost complete collapse of the left lung is being maintained by weekly injection of air into the pleural cavity.

At the present time the patient is afebrile. She has gained twenty pounds since her illness nine months ago. The first examination of her sputum at Bellevue Hospital in May was positive for tubercle bacilli, but all subsequent examinations, including concentrates of the sputum and gastric contents, have failed to reveal these organisms. The patient coughs very slightly, expectorating a little sputum but no blood. She becomes fatigued and somewhat dyspneic with moderate activity.

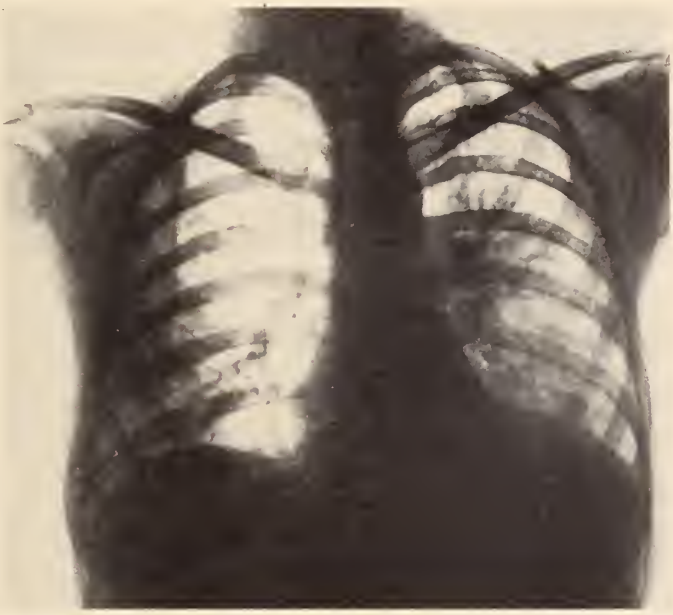

FIG. 1. Pneumonic infiltration of the left lower lobe. A later roentgenogram after pneumothorax showed that the lesion was confined to the left lower lobe, the left upper lobe being uninvolved.

but it must be remembered that she has an almost complete pneumothorax on one side. She suffered an upper respiratory infection in December without apparent ill effects. There is no evidence of the spread of this infection to the other lung.

COMMENT

Primary pulmonary tuberculosis of the lower lobe has been discussed by Hamilton and Fredd (1), by Reisner (2), by Weidman and Campbell (3), and by others. Its incidence was formerly stated to range between 0.3 per cent and 0.8 per cent of all cases of chronic pulmonary tuberculosis. However, Ross (4) reported the presence of pulmonary lesions primarily or predominantly in a lower lobe in eleven out of sixty nurses with pul-

monary tuberculosis. This suggests that primary tuberculosis of the lower lobe occurs more commonly than is generally believed and that its incidence would be higher if the presence of tuberculosis were recognized early before the lesions were widespread throughout the lungs. In the cases reported by Ross it was possible to make relatively early diagnoses, because the nurses were in close contact with diagnostic facilities. As a rule, when pulmonary tuberculosis is first recognized, the lesions are found in several lobes and it is often difficult to determine the primary site of origin.

Usually the earliest lesions of adult pulmonary tuberculosis with clinical manifestations are found in that part of the infraclavicular region which is supplied by the paravertebral branch bronchus of the upper lobe. The cause for this localization is still a moot point. But it is interesting to note that tuberculosis of the lower lobe, whether primary, or secondary to upper lobe tuberculosis, begins usually in the upper portion of the lower lobe. This area is supplied by the apical branch bronchus of the lower lobe which has the same anatomic direction as the paravertebral branch of the upper lobe. This localization accounts for the fact that postero-anterior roentgenograms of patients with lower lobe tuberculosis reveal shadows which are situated close to the hilus or in the middle lung fields, their presence in the lower lobe being clearly demonstrable only in lateral films. Thus, many cases of lower lobe tuberculosis have been described as hilar tuberculosis, epituberculosis, or a childhood form of tuberculosis. However, pathogenetically and clinically these cases of lower lobe tuberculosis do not differ from other cases of adult chronic tuberculosis elsewhere in the lung.

Lower lobe tuberculosis occurs predominantly in females. Reisner has explained this observation by assuming that respiration in women is chiefly of the costal variety, the diaphragm being relatively immobile, and that as in upper lobe tuberculosis the infection starts in pulmonary areas which are least ventilated. Neither the assumption that tuberculosis begins in the least aerated portions of the lung nor that the women with lower lobe tuberculosis have relatively inactive diaphragmatic respiration are generally accepted. Etiologically interesting is the claim that lower lobe tuberculosis tends also to occur in men with pulmonary silicosis (5) and in patients with diabetes (6).

Several features in the case herein described differ apparently from the usual cases of lower lobe tuberculosis described in the literature. In this case, the lesion was an exudative one occupying the entire left lower lobe and not a localized infiltration in the upper part of the lower lobe adjacent to the hilus. This close resemblance to croupous lobar pneumonia obscured the tuberculous etiology even after roentgenologic examination. Cases of complete lower lobe tuberculosis have also been occasionally described, but almost invariably at the first examination there is a cavity

which occurs early and develops rapidly. Such lesions are often mistaken for pulmonary suppuration. The absence of cavitation in this case probably indicates that we are dealing with a much earlier exudative stage of the disease than is usually recognized. The failure of cavitation to develop later may indicate that there was a gelatinous pneumonia with little or no caseation, or that it was avoided by the prompt institution of pneumothorax therapy.

The definite diagnosis of lower lobe tuberculosis as of all pulmonary tuberculosis depends on finding tubercle bacilli in the sputum. In cases with lesions in the upper lobes of the lungs, it is likely that the sputum will be examined regularly for tubercle bacilli. However, when only the lower lobes are involved, such examinations are usually entirely omitted or made superficially; tuberculosis in this location is apt to be overlooked. Thus, in this case the sputum was not examined until the patient was in the hospital for five days because it was assumed that a lower lobe consolidation without cavitation indicated a pneumococcic etiology. According to Hamilton and Fredd (1), an additional difficulty in the diagnosis of lower lobe tuberculosis arises from the fact that the sputum, in such cases, is frequently negative since the lesions are less "open" than in the usual case of active pulmonary tuberculosis. Despite this, however, the frequency of discovery of lower lobe tuberculosis will undoubtedly be increased if the sputum is always examined for tubercle bacilli in pulmonary lesions of the lower as well as of the upper lobes.

When the above patient was first seen, the diagnosis of pulmonary tuberculosis rather than that of pneumonia was suggested because of the following considerations: A clinical onset which was not typical of pneumonia, the patient's relative well-being in spite of high fever, the absence of tachypnea or other respiratory symptoms, and physical signs which differed somewhat from those of a pneumococcus pneumonia of twenty-four to thirty-six hours duration. Often at this stage of the latter disease, there is only dullness on percussion and a diminution and roughening ing of the breath sounds. If râles are present, they are of the fine, crepitant variety and sparse in number. If signs of consolidation, such as bronchial breathing have developed, râles are usually absent. In this case, there was an extensive area of dullness over the left lower lobe, the breath sounds were bronchovesicular or bronchial over this area, and most important, there were numerous crepitant and subcrepitant râles which were coarser than those heard in pneumococcus pneumonia.

After the patient's admission to the hospital, the likelihood of a tuberculous etiology for the pneumonia was indicated by the relatively low white blood count (11,000) in relation to the high fever, the absence of herpes labialis, the prolonged duration of the fever, the lack of response to sulfapyridine and the positive tuberculin reaction. The isolation of a type 20 pneumococcus from the sputum was not etiologically significant because

it was not obtained by direct Neufeld examination of the sputum, but only after incubation of the sputum in a mouse. The higher types of pneumococci are common inhabitants or secondary invaders of the respiratory tract and are not usually of clinical importance unless observed in the original sputum.

The early recognition of the tuberculous nature of the pulmonary infection and the institution of appropriate treatment account for the excellent therapeutic result and for the absence of cavitation or extension of the disease to other portions of the lung. Had the patient continued to be treated as a case of lobar pneumonia and later as one of unresolved pneumonia, as often happens, it is possible that the diagnosis of tuberculosis would have been made, and therapy given at a much later time when the disease was more extensive and the chance of cure less favorable. The prompt administration of pneumothorax is not a universally accepted treatment for acute exudative tuberculosis. In this case it effected a brilliant therapeutic result.

SUMMARY

1. A case is reported of exudative pulmonary tuberculosis of a lower lobe simulating pneumococcus lobar pneumonia.

2. A clinical diagnosis was made early on the basis of the general appearance of the patient and certain atypical physical signs. Later this was confirmed by discovery of tubercle bacilli in the sputum.

3. Because of the location of the lesion in a lower lobe and before tubercle bacilli were found, some observers believed this to be a case of pneumococcus pneumonia which seemed to be confirmed by the typical roentgenogram of a pneumonic consolidation without cavitation limited to the lower lobe. Sulfapyridine was administered in large doses but proved ineffective.

4. By means of artificial pneumothorax, almost complete collapse of the left lung was obtained. Cavitation and spread of the lesion to other lobes failed to develop. The patient has now been afebrile and her sputum free from tubercle bacilli for seven months. Despite her pulmonary collapse, she has only mild symptoms such as fatigue and slight cough.

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RIGHT LOWER QUADRANT SUPPURATION COMPLICATING CARCINOMA OF THE COLON ASCENDENS: REPORT OF TWO CASES

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Two cases of carcinoma of the ascending colon are presented in which the early symptoms suggested a suppurative process in the right lower quadrant. Subsequently, operation and observation proved both cases to be carcinoma.

Case 1. *History* (Adm. 442387) This patient, a white married man, aged 31, was admitted to The Mount Sinai Hospital on June 22, 1939 with a chief complaint of a draining abdominal abscess. He was perfectly well until January 1939 when he developed upper abdominal cramps. The pains at first had no relation to meals. One month after the onset, however, they came on one hour after meals and lasted a few minutes to half an hour. At this time he also noticed gaseous distention and "heartburn" immediately after eating. In February 1939 he experienced anorexia and lost weight, and shortly afterwards began to vomit frequently. Late in March he became aware of a tender mass in the right lower quadrant and was admitted on April 3, 1939 to a local hospital, where a preoperative diagnosis of appendiceal abscess was made. A laparotomy through a right rectus incision was performed soon after admission. The surgeon's report stated "that the appendix seemed to be normal but at the hepatic flexure a densely adherent mass the size of a grapefruit and presumably an abscess was seen." The mass was proved to be an abscess and was drained. Post-operatively the patient developed a superficial abdominal abscess in the right lower quadrant. This required two additional periods of hospitalization with incision and drainage performed on both occasions. Early in June the abscess was again incised and drained by a private physician. During this period the patient had frequent bouts of nausea and vomiting. There was no history of diarrhea or melena. The family and past history were non-contributory except for the fact that the patient's mother died at the age of 49 years of carcinoma of the rectum.

On admission to The Mount Sinai Hospital the patient appeared chronically ill and showed obvious weight loss. The temperature was 100.6°F.; respirations 20 per minute; pulse 80 per minute and the blood pressure was 135 systolic and 65 diastolic. The essential physical findings were confined to the abdomen. On the right side of the abdomen at the level of the umbilicus there was a grapefruit-sized mass at the center of which was a recent rectus incision. Two fistulous openings were seen at the lower angle of the incision, draining fecal material.

Laboratory data: The white blood count was 11,300 with 74 per cent neutrophiles. The hemoglobin was 50 per cent (Sahli). The urine showed a trace of albumin but no sugar. The sediment was normal. Chemical examinations of the blood revealed no abnormalities. The stool gave a two plus reaction to the Guaiac test. Biopsy of fragments of the fistulous tract revealed mucous cell carcinoma. A barium meal examination was done and revealed a pressure defect due to an extra-

gastric mass involving the antrum and the body of the stomach. At the twenty-four hour examination the proximal one-third of the colon showed a defect either "due to an incomplete filling or a neoplasm" (Fig. 1). Since the presence of carcinoma had been established, a diagnosis of carcinoma of the ascending colon was made.

Course: The patient was considered inoperable because of invasion of the abdominal wall and because of his poor general condition. He was discharged on

FIG. 1. Roentgenogram 24 hours after barium meal administration showing a defect of the proximal one-third of the colon "due either to an incomplete filling or a neoplasm."

July 4, 1939 with no improvement after receiving a short course of radiotherapy. He went downhill quickly and died at a local hospital in September. An autopsy was not performed.

Case 2. *History:* (Adm. 443617) A white, married female; age 42. This patient was admitted to The Mount Sinai Hospital on July 23, 1939. The chief complaint was abdominal pain and diarrhea. The patient had been quite well until two weeks before admission when she first noticed generalized abdominal cramps, more severe on the left side. She had diarrhea for several days and consulted a private physician who diagnosed colitis and gave her powders with complete relief of her symp-

toms. One week before admission the generalized abdominal cramps returned and for the first time she passed a small quantity of bright red blood by rectum. She took her previously prescribed powders again with complete relief until one day before admission. At this time the abdominal cramps returned, now more severely on the right side. She passed bright red blood for the second time. A private physician was called at 5 o'clock the next morning due to the severity of the abdominal pain. He immediately sent her into the hospital. The patient's past

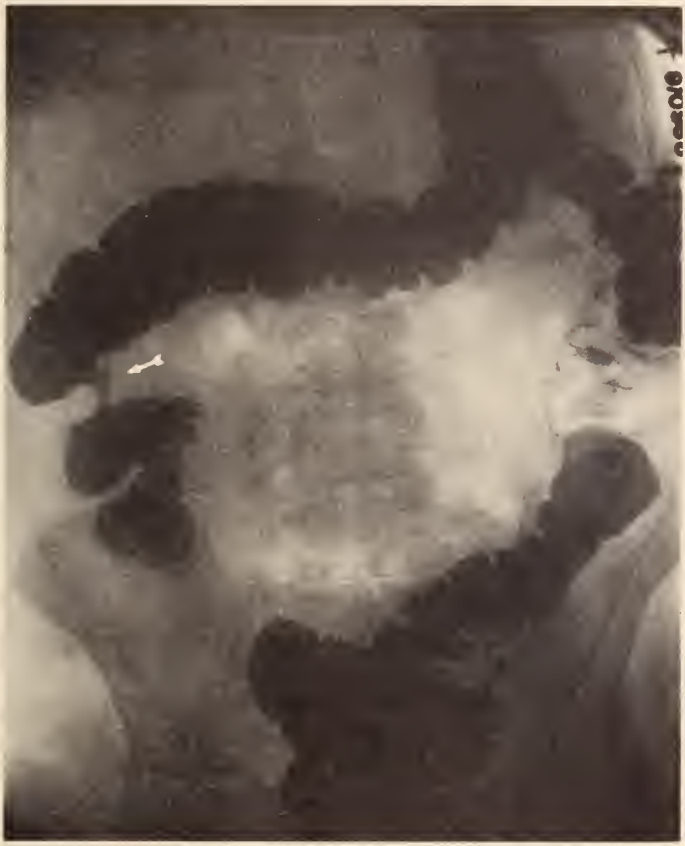

FIG. 2. Roentgenogram after barium enema administration showing a "stenosing lesion of the ascending colon with the appearance that of a neoplasm approximately two inches in length and moderately obstructing to the passage of barium."

history revealed that a supravaginal hysterectomy and bilateral salpingo-oophorectomy had been performed eight and a half years earlier at The Mount Sinai Hospital. Two and a half years before admission there had been a typical gall-bladder attack with gall-bladder calculi demonstrated by X-ray examination. On a fat free diet she had remained in good health until the present illness. The remainder of the past history and the family history were non-contributory.

On admission the temperature was 100.6°F.; the pulse 96 per minute; the respiration 22 per minute and the blood pressure was 140 systolic and 95 diastolic. The patient was moderately obese and acutely ill. The essential physical findings were

confined to the abdomen which was distended moderately and tender throughout. Tenderness was marked in the right lower quadrant with some muscle spasm and guarding. The rectal examination was negative except for the presence of tarry material on the gloved finger. The Guaiac test was strongly positive.

Laboratory findings: The hemoglobin was 43 per cent (Sahli); the white blood count was 22,800 with 80 per cent neutrophiles. The urine showed a trace of albumin but no sugar. The sediment revealed an occasional hyaline cast. A diagnosis of carcinoma of the colon with intussusception was entertained. On the day of admission an exploratory laparotomy was performed through a lower right rectus incision. The cecum was seen to be distended and deeply placed. Retrocecally, there was found a short, curved, acutely inflamed, pus-filled appendix. An appendectomy was performed in the usual manner and the patient was returned to the ward in good condition.

Course: The patient did fairly well albeit she ran a low grade fever. One week after operation she developed a profuse fecal leak from the upper and lower poles of the wound. The stool continued Guaiac positive and the hemoglobin varied between 47 per cent and 53 per cent. On August 16 a barium enema was administered and showed a "stenosing lesion of the ascending colon with the appearance that of a neoplasm approximately two inches in length and moderately obstructing to the passage of barium" (Fig. 2). The fecal fistula continued to drain and on September 2, 1939 a second operation was performed. A large mass was felt in the right lower quadrant and the operating surgeon felt quite definitely that a carcinoma of the ascending colon was present. Due to agglutination of loops of ileum against the region of the ileo-cecal valve, an ileo-sigmoidostomy without exclusion had to be performed. The patient did well postoperatively although the fecal leak continued. On October 4, 1939 the patient was again explored and this time an inoperable carcinoma of the ascending colon was seen with liver metastases. At the present writing the patient is still in fairly good condition. At no time had she become obstructed, apparently due to the fact that the draining fistulae acted as a cecostomy.

DISCUSSION

These two cases are presented to illustrate the fact that carcinoma of the colon may occasionally simulate and/or be complicated by an acute suppurative process. In the first case a diagnosis of acute appendicitis was made in a young man of 31 years. At operation an abscess in the right lower quadrant was found although the appendix was apparently normal. The abscess formation was due in this case to perforation of a carcinoma of the ascending colon. This man ultimately developed a fecal fistula. Cases of abscess formation in the right lower quadrant resulting in fecal fistulae following perforation of a carcinoma have been recorded by Bevan (1), Bailey (2), Bargin (4) and others. In a series of 1502 consecutive cases of carcinoma of the colon at the Mayo Clinic 141 were diagnosed at operation as complicated by perforation. Thus, the condition is not infrequent.

In the second case an acutely inflamed appendix was found. Again the colonic carcinoma was not the reason for the operation. The symptoms were traceable to the two diseases: acute appendicitis and carcinoma. Feldman (5) describes a case in which the appendix was removed and a

secondary operation was required a few months later to remove a carcinomatous growth of the caecum. Ogilvie (6) cites 11 cases of the colon in which the appendix had been previously removed. The relationship is not clear; it seems most likely that the findings are coincidental. However, it is possible that an obstructing carcinomatous lesion of the ascending colon may cause a reflux of fecal contents into the appendix with resulting stagnation and infection.

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COMMON DUCT STONE SIMULATING "CHOLANGITIS LENTA"

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Schottmuller, in 1921, described a clinical entity which he termed "cholangitis lenta" because of its apparent similarity, clinically and bacteriologically, to endocarditis lenta (1). Thus, in both conditions, there is present a generalized infection which is insidious in onset and is marked by a protracted and irregularly febrile course; also in both conditions, the streptococcus viridans is the organism held responsible for the disease. Whereas in endocarditis lenta the shock organ is the endocardium, as the name implies, in cholangitis lenta the smaller biliary radicles bear the brunt of the infectious process.

Since the condition was originally described a number of reports have appeared, chiefly in the German literature, describing additional cases. But a brief survey of these reports shows that, while the reported cases have many clinical features in common, there is no agreement concerning their bacteriological and pathological features. Because of these discrepancies, LaManna (2) believes that "cholangitis lenta" should not be conceded the status of a clinical entity because, he claims, a clinical entity should have definite and constant bacteriological and pathological findings.

As originally described, and reported by others, the clinical course of cholangitis lenta is usually protracted and marked by recurrent episodes of chills, fever, generalized aches and pains and a progressive secondary anemia. In these respects the condition is similar to endocarditis lenta (subacute bacterial endocarditis). Jaundice and hepatomegaly are usual, although not essential for diagnosis, while splenomegaly and ascites may also be present (3).

One of the requisites for diagnosis in Schottmuller's original series was the presence of the streptococcus viridans in the patient's blood or bile. Since that time, however, the reported cases have failed to fulfill this requirement. Meyer (4) states that Schottmuller's streptococcus viridans undoubtedly included other organisms, particularly the enterococcus. When the streptococcus viridans was intravenously injected into experimental animals, he could not recover the organism in the bile, from which he concluded that reasonable doubt existed whether the organism could ever reach the biliary system from a blood stream infection in man. On the other hand, he contends, enterococci are the normal inhabitants of the intestinal canal and can easily find their way into the biliary tract, either by direct invasion through the common bile duct or by way of the

lymphatic or venous routes. At any rate, since Schottmuller's report, the green streptococcus has not been found with the constancy one would expect in a clinical entity and, furthermore, various other organisms have also been indicted as a cause for the disease. Loewenhardt (5) cultured a hemolytic streptococcus from one of his cases while Umber (6) found paratyphosus B and Hedinger (7) reported B. coli as the causative agent. Evidently, the bacteriological basis for the diagnosis of cholangitis lenta is not quite definite.

When we turn to examine the pathological findings in the reported cases we are met with a series of varying pictures which again cause us to wonder whether "cholangitis lenta," as a clinical entity, really exists. In several of the reported cases only the clinical course of the patient is given as basis for the diagnosis without substantiation by bacteriological or pathological evidence. In other cases various types of liver disease, including gallstones and carcinoma, and even some generalized infections without any hepatic involvement at all, are found to have produced clinical pictures interpreted as cholangitis lenta. Eickoff's case (3) was secondary to stones in the common duct; Loewenhardt's case revealed pericholangitic abscesses secondary to a purulent cholecystitis (5); other cases presented fatty degeneration of liver cells, lymphocytic infiltration in the periportal spaces, and one showed an adenocarcinoma of an hepatic duct with secondary involvement of the intrahepatic biliary tree (8). Klemperer (9) states that a diagnosis of cholangitis or cholangiolitis is justified only if inflammatory cells are found in the lumen or walls of the biliary canaliculi. It is thus seen that some of the reported cases did not even have a cholangitis.

LaManna believes the term "cholangitis lenta," if used at all, should be reserved to describe a clinical picture where chronic sepsis exists in association with biliary tract inflammation, but where we can find no apparent extrinsic cause for this inflammation, such as stone or tumor. He reports one such case (2) which, on pathological examination, revealed multiple pericholangitic liver abscesses from which B. coli and enterococci were grown.

We are now reporting a case which fits into the loosely defined category of "cholangitis lenta" insofar as it presents the clinical picture of that condition. However, like most of the cases reported in the literature, its characteristic features were found to have been caused by an extrahepatic factor, a calculus in the common bile duct, and not by a blood-borne infection of the smaller biliary radicles. Clinically, bacteriologically and even after two exploratory laparotomies, this case satisfied most of the requirements for the diagnosis of "cholangitis lenta," and it would have gone down as such in the records were it not for the post-mortem findings. Like the words "essential" and "idiopathic" it seems that the term "cholangitis lenta" is one used to salve one's diagnostic conscience

when the exact nature of some biliary tract infection remains shrouded in obscurity.

CASE REPORT

History (Adm. # 435823) M. L., a married, 65-year old cabinet-maker, was admitted to the medical ward with a 7-month history of recurrent attacks of chills and fever without any localizing complaints. The patient's first symptom was a severe shaking chill accompanied by nausea and followed by a temperature rise to 104°F. This temperature rise lasted about twelve hours and left the patient exhausted but without any definite complaint. He was then entirely asymptomatic for two weeks when he experienced another attack which was similar to the first in all essential details. For the following four months the patient continued to have episodes of chills and fever at two week intervals. All the attacks lasted about twelve hours and were associated with nausea; vomiting also occurred on occasion. In the three months preceding admission to the hospital these episodes became increasingly more frequent, so that whereas at the onset they occurred every two weeks, they began to recur at weekly intervals, then twice a week, and, just before admission, there was one occasion in which the attacks took place daily for six days. There was never any localizing pain or discomfort, and the only suggestive feature in the entire history was the appearance of blood-tinged mucus in the stools during the week before entry into the hospital. The patient lost 30 pounds during his 7 month illness and became gradually weaker and more cachectic.

Of note in his past history was an attack of malaria at the age of 5, typhus fever at 22 and pleurisy with effusion at 30. These illnesses were all apparently without sequelae. Both of the patient's parents had died of pulmonary tuberculosis.

Examination. On admission, the patient was somewhat emaciated. There was moderate pallor of the skin and mucous membranes. There was no icterus or cyanosis. The right eye had previously been operated on for the removal of a cataract. The fundi showed moderate temporal pallor. The teeth were carious. The tonsils were reddened and cryptic. The lungs were clear except for transient moist râles at the left base. The heart revealed no abnormality by percussion or auscultation. His blood pressure was 130 systolic and 80 diastolic. There was moderate tenderness over the right lobe of the liver on percussion but the liver was not enlarged. Neither the spleen nor other viscera were felt. There was no local or generalized lymphadenopathy.

Laboratory Data. Hemoglobin was 89 per cent; white blood cells 13,000 of which polymorphonuclear lymphocytes constituted 80 per cent. Immediately after a chill, at the height of the temperature rise, the white blood cell count rose to 34,000 with 83 per cent polymorphonuclear lymphocytes. The urine concentration test showed the specific gravity to be 1.030. The urine contained traces of albumin with occasional white blood cells in the sediment. There was no bile in the urine. Examination of the stools was negative for occult blood, ova or parasites. Blood chemistry was normal and never showed any increase in the icteric index or bilirubin content. Repeated blood examinations for malarial parasites were negative, as were four blood cultures. The patient's blood showed no agglutination against B. typhosus, paratyphosus, abortus, melitensis and five different strains of dysentery organisms. A Rehfuss test meal revealed complete absence of free hydrochloric acid with a total acidity of 24. On two occasions bile obtained by biliary drainage was cultured, and on both occasions enterococci and B. coli grew out. X-ray examination of the chest and abdomen revealed no abnormalities, but a cholecystogram, performed after the oral administration of tetro-iodo-phenolphthalein, failed to visualize the gallbladder; thus indicating some impairment in biliary tract function.

While in the hospital the patient continued to have episodes of chills and fever, and because of the history of bloody mucus in the stools, sigmoidoscopy was performed. The instrument was passed 25 cm. and revealed an inflamed and granular mucosa which bled easily on manipulation. No ulcers were seen. A piece of rectal mucosa, removed for biopsy, was reported as showing chronic, non-specific inflammation. No amebae were seen.

Course. Because of the persistence of liver tenderness, the recurrent chills and fever and the sigmoidoscopic evidence of colitis, the patient was suspected of having an amebic abscess of the liver secondary to amebic involvement of the large bowel. He was therefore given a course of emetine, one grain daily for ten days, without any improvement. In view of the lack of progress made with medical measures, the surgical service was consulted: Operation was decided upon for the purpose of draining the suspected liver abscess.

The operation was performed by Dr. R. Colp. The liver was found to be normal in size and appearance, as was the spleen. The subphrenic spaces were explored and found to be clear. The inferior vena cava was palpated and yielded its characteristic venous thrill, thus ruling out thrombophlebitis. The stomach, intestines and kidneys revealed no abnormality. The gallbladder was thin-walled and contained no stones but it was markedly distended, definitely beyond physiological limits. The common bile duct was not dilated and contained no calculi. Despite the absence of any obstructing factor, such as stone or tumor, the surgeon felt that the distended gallbladder indicated some biliary stasis which, perhaps, was responsible for involvement of the intrahepatic portion of the biliary system resulting in the symptom-complex presented by the patient. A cholecystostomy was, therefore, performed to obtain free biliary drainage and a small section of liver tissue was removed for biopsy.

Microscopic examination of the bile aspirated from the gallbladder at operation showed moderate numbers of pus cells and much amorphous debris. Culture, however, revealed the presence of B. coli, enterococci and B. welchii. This culture was repeated a week later and verified. The biopsied liver tissue was reported as showing "considerable numbers of polymorphonuclear leucocytes in the periportal spaces" and also evidence of liver cell regeneration (fig. 1).

During the first week post-operatively the patient developed an extensive sacral decubitus which required wide incision and drainage. Following this procedure the temperature promptly dropped to normal levels and remained so until the day of discharge, six weeks later (fig. 2). The cholecystostomy drainage tube was kept in situ for five weeks. The bile, which was thin and watery during and immediately after the operation, gradually became darker and more viscid. After the first week repeated cultures of the bile were sterile, and stained smears of the sediment revealed only occasional pus cells.

Six weeks after operation the patient's clinical course had been such that he was considered to be clinically cured. He had experienced no further chills or fever, his appetite and general appearance had gradually improved and he was able to leave his bed and walk about for the first time in more than four months. He was therefore discharged to the care of his private physician. The cholecystostomy tube had been removed and the resulting drainage tract was almost entirely healed. The patient was considered to have been a case of biliary tract infection, most likely one of so-called "cholangitis lenta," cured by adequate biliary tract drainage. It is interesting to note that on the morning of his discharge the patient experienced a mild chilly sensation for the first time since the operation, and his temperature, immediately following the chill, was found elevated to 102°F. He felt well, however, and insisted on leaving the hospital, contrary to medical advice.

One week later, while at home, the patient experienced another shaking chill

followed by a temperature rise to 102°F., and he was immediately readmitted to the hospital. Since the cholecystostomy tract had been closed for about a week it was thought that reestablishment of biliary drainage might effect an improvement in his condition. This was done by inserting a tube through the scar of the drainage tract and the patient remained afebrile and asymptomatic until his discharge one month later.

Two weeks later he began to experience recurring attacks of chills and fever and he was admitted to the hospital for the third time. The physical findings now included a tender liver edge palpable two fingerbreadths below the costal margin, and moderate upper abdominal spasm and tenderness. There was no jaundice and the blood icteric index was normal. The patient was taken to the operating room and the right lobe of the liver was aspirated in several places in an attempt to find or rule out the presence of a liver abscess. No pus was found, but several fragments of liver tissue were obtained which, on microscopic examination, showed "intensely acute inflammation and focal parenchymal necrosis suggestive of suppuration." On the basis of this finding, another course of emetine was administered.

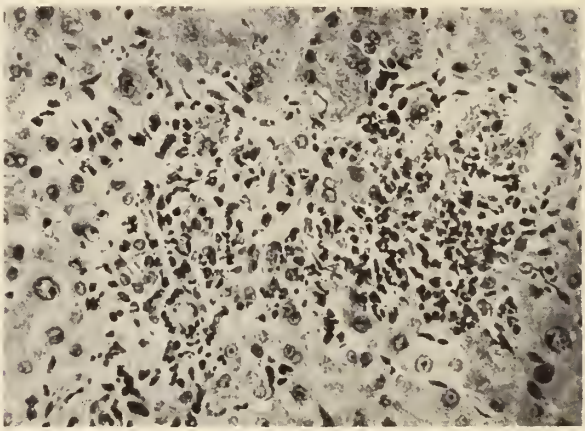

FIG. 1. Section of liver removed at operation showing leucocytic infiltration in periportal areas.

The patient's symptoms and signs continued unchanged, however, and it was deemed advisable to perform another exploratory laparotomy in the hope of finding some remediable lesion. On opening the peritoneal cavity about 500 cc. of non-foul, cloudy yellow fluid gushed forth from the right subphrenic space. The liver appeared grossly normal but the tissues in the gastrohepatic omentum were markedly edematous. The gallbladder was thickened and distended, and the common bile duct was dilated to about six times its normal size. The common duct was opened and explored, and found to contain an appreciable quantity of "bilirubin sand", which was removed. A probe could not be passed into the duodenum because of the marked edema present so that a T-tube was left indwelling to drain the biliary system.

Despite apparently satisfactory biliary drainage post-operatively, the patient became progressively more cachectic and died six days later in circulatory collapse. Post-mortem examination disclosed a small stone in the retroduodenal portion of the common bile duct, surrounded by and buried in intensely inflamed and edematous tissues. There was also found a suppurative thrombophlebitis of the intrahepatic branches of the portal vein with multiple small liver abscesses.

SUMMARY

A brief description of "cholangitis lenta" is presented which purports to show that most of the cases so listed in the literature have really been cases of extra-hepatic biliary extract disease with secondary involvement of the finer biliary radicles.

A case in point, considered fairly typical of "cholangitis lenta," is described. Two exploratory laparotomies were performed to rule out an extrinsic cause for the biliary tract infection. Although no such extrinsic factor could be found, post-mortem examination disclosed the symptom-complex to have been caused by a deeply hidden and inaccessible calculus in the retroduodenal portion of the common bile duct.

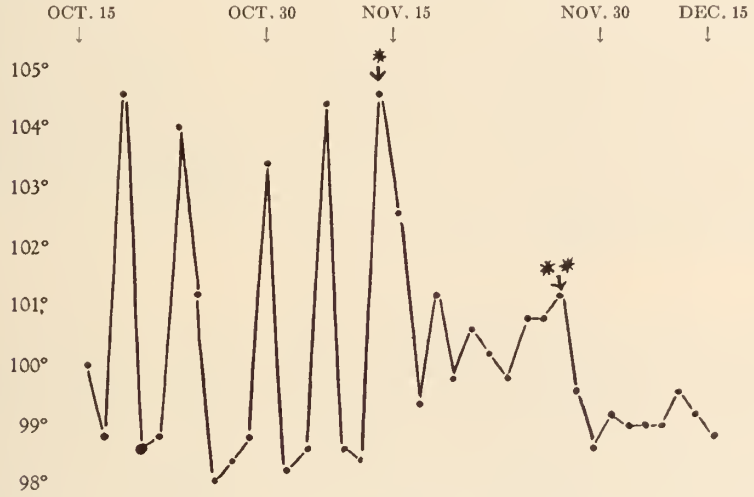

FIG. 2. Temperature chart of patient's first hospital admission showing prompt response after cholecystostomy (*) and after drainage of decubitus abscess (**).

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SELECTED TOPICS IN TOXICOLOGY[1]

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In the preceding lecture I described the different ways in which poisons are destroyed in the organism. We now come to the problem of elimination of poisons through excretion which is of great importance. No matter how significant are the numerous ways utilized by the organism in the destruction of endogenous and exogenous poisons, it must never be forgotten that this capacity is a very limited one. The organism, as a rule, is able to destroy only small quantities of poisons. A striking example is the power of the organism to oxidize alcohol; the human body oxidizes only 10 cc. of alcohol an hour and this rate can not be increased even by larger doses. The chief means of the body to render poisonous substances ineffective is by eliminating them thoroughly.

SPEED OF EXCRETION

Since the noxious effect of the poison depends upon its concentration in the blood and tissues, the speed of excretion is the chief factor determining its effect. All substances which are eliminated slowly, such as strychnine, digitalis, bromides and the salts of boric acid result, therefore, in a *cumulative effect.* Such a prolonged effect is often desirable, as in the case of bromides in the treatment of epilepsy or in the employment of digitalis in cardiac disease. Such effect is also desirable in disinfectants such as mercury or arsenic compounds. *Lead* and *arsenic*, too, are slowly eliminated and thus, they accumulate. This was shown by the lead epidemic in Sheffield caused by the contamination of the drinking water in which one part of lead was contained in 500,000 parts of the water. A similar epidemic of arsenic poisoning in Manchester occurred when the concentration of arsenic in beer was one to three million. Doses like these are of course quite ineffective when taken occasionally or for only a short time. Lead acetate, taken in doses of even three to four grams daily for a period of time up to ten days in succession, has no effect (1). When taken over longer periods of time, e.g., for many months as in the case of the Manchester and Sheffield epidemics, the most minute amounts of arsenic and lead have great effects.

[1] The third of a series of lectures introducing discussion of selected topics in toxicology, delivered before The Mount Sinai Hospital Staff during January and February, 1940.

Another striking example of delayed poisoning is *radium* poisoning. Radioactive paint, containing 0.7 to 3 mg. of radium per 100 grams, caused in workers symptoms characterized by general weakness, aplastic anemia, lymphatic leukemia, and necrosis of the jaw, this occurring from one to several years after the beginning of their employment (2).

An attempt has even been made for therapeutic purposes to prolong the action of some swiftly acting hormones. In the case of insulin, for instance, in order to reduce the speed of its elimination, it is introduced in the combined form of *protamine zinc insulin*. On the other hand, hormones like those of the *thyroid gland*, by their qualities, act slowly for periods of weeks or longer.

Other drugs, however, ought to be eliminated quickly. *Hypnotics* should act only a few hours, or even for a shorter period, when they are used as anesthetics. Fatal accidents are apt to happen, however, in cases in which we have no means of influencing or controlling the rate of elimination of the drug employed. That is why so many accidents occur in the administration of hypnotics as narcotics. Moreover, the wide individual variations of the human body in response to drugs are to be borne in mind. This is well illustrated by the accompanying diagrams, demonstrating individual variations in the effects of sodium salicylate (fig. 1) and sodium amytal (fig. 2).

MODES OF EXCRETION

The excretion of drugs is effected through the kidneys, the intestines, the lungs and, to some extent through the saliva, the bile and the skin.

The kidneys. This organ shows large differences in the excretion of various substances quite independently of diuresis. An example of this is the excretion of creatin, used in the well known test of kidney excretion. Creatin excretion is in direct and exact ratio to the creatin-concentration in the blood and is absolutely independent of its concentration in the urine. The same applies to the salts of boric acid (3). The *rapid* excretion by the kidneys of certain complex organic compounds of iodine as after intravenous injection of sodium-iodopyridon-acetate (Uroselectan, Jopax) or others (Perabrodil) is of great value in radioscopy of the urinary system.

The lungs. Elimination through the lungs depends upon: 1) cardiac output, 2) volume of respiration, 3) concentration of the inspired gas, and 4) the boiling point of eliminated gaseous substances.

Ether, for instance, with a boiling point of 35° centigrade, is completely eliminated within one hour, and its concentration in blood drops, after a few minutes, to a non-toxic level. *Chloroform*, however, with a boiling point of 61° centigrade, takes many hours (6 to 7) to be completely eliminated. This indicates the danger of its application (table 1). The importance of a sufficient cardiac output is indicated by the fact that rapid elimination through the lungs is enhanced by cardiac remedies, which

increase the cardiac output and bring more blood-saturated toxic substances to the lungs. This effect can not be achieved by artificial respiration alone.

Digestive tract. Elimination through the digestive tract starts already with the secretion of saliva. Not only *bromine, iodine, mercury, bismuth*

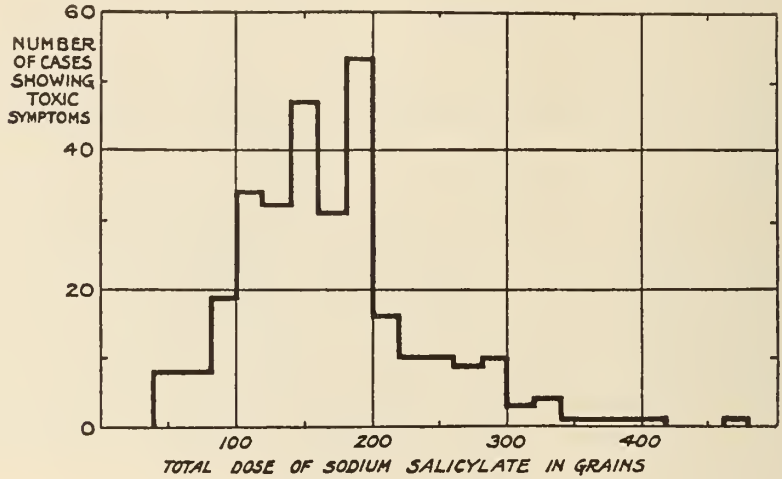

Fig. 1. The individual variation amongst 300 males in the amount of sodium salicylate taken before toxic symptoms appeared (Hanzlik (1913)). From A. J. Clark: Applied Pharmacology, London, 6:17, 1937.

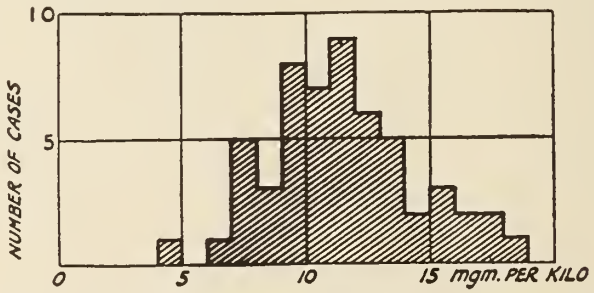

Fig. 2. Dosage of sodium amytal (mgm. per kilo) needed to produce adequate narcosis when given by slow intravenous injection to 55 obstetric cases (Paxson (1932)). From A. J. Clark: Applied Pharmacology, London, 6:18, 1937.

and *lead* are eliminated in saliva, but also organic substances like *rhodan*, and alkaloids like *morphine* and *heroin*. This excretion of heroin by the saliva has helped in the detection of doping of race horses; this is easily proved by testing the saliva of the horse. It is also known that morphine is excreted through the stomach and the intestines, even when the alkaloid is given subcutaneously. Many dyes and other substances are excreted in the bile; as in the case of *methylene blue* and *tetraiodophenolphthalein* (4), the latter not passing through the kidneys. *Hexamethylene tetramine* and

various metals like *lead, silver, iron* and *copper* behave the same way. It must be mentioned finally that *arsenic* and *mercury* are excreted through the large bowel and can occasionally cause ulcerations, the demarcation line being the ileo-cecal valve.

The skin. The skin also plays an important role in the elimination of some poisons such as *volatile oils, sodium chloride, phenol,* and *salicyclic acid. Heavy metals,* particularly arsenic compounds, are deposited in the horny layers of the skin and in the hair and are eliminated in this way from the organism.

TABLE 1

Speed of excretion of chloroform and ether after narcosis

TIME AFTER END OF NARCOSIS	AMOUNT OF ANESTHETICS IN BLOOD IN PER CENT	
	Chloroform narcosis	Ether narcosis
0 minutes	0.0595	0.159
3 minutes		0.108
5 minutes		0.080
15 minutes		0.058
30 minutes	0.023	
1 hour	0.018	0.021
2 hours		0.004
3 hours	0.0075	
7 hours	0.0015	

Mammary glands. The excretion of poisons through the milk glands is highly significant in infant nutrition. *Ether, chloroform, alcohol, arsenic, mercury, bromides, iodine,* and *lead;* also *morphine* and *nicotine* appear in the milk if the mother received any of them. Fatal accidents have occurred when this factor has been overlooked.

SYNERGIC AND ANTAGONISTIC ACTION OF POISONS

We must also consider the reactions of the organism when several poisons take simultaneous effect. Such combinations of poisons and remedies have been used since ancient times as in the case of the substances contained in *opium* or *digitalis* and the *belladonna drugs.* In this connection, I wish to remind you of the newly used *combinations of the pure alkaloids:* scopolamine, hyoscyamine, and atropine in the treatment of athetosis of sufferers from chronic encephalitis; also of the sleep-inducing combination of morphine and scopolamine; of the numerous *pain relieving mixtures* of caffeine, pyramidon, phenacetine, quinine, codeine, and aspirin; of the *anesthetic mixtures* of ether and barbiturates or avertin; of the *local anesthetic combination* of cocaine and adrenalin and of the use of *purine derivatives in heart therapy* (caffeine, aminophylline) with *digitalis or strophanthin.* These few examples of combinations can be multiplied at

will in all the different spheres of clinical therapeutics (5). According to Buergi, remedies with the same effect will, as a rule, cause an additive result if they have the same pharmacological point of attack, and a hyperadditive result if they have different points of attack (6). We speak in the first instance of *synergism*, as in the additive rise in the effect of the narcotics of the fat series (chloroform and ether), in the second instance, we speak of *potentiation* as in the combination of morphine and scopolamine which gives a sedative effect far surpassing the simple effect of summation.

Several combinations of poisons, show in effect, a very much greater toxic danger, as for instance *alcoholism* and *lead poisoning*, or *alcoholism* and *anilin poisoning;* similarly, as already mentioned above, combinations of *sulfanilamide with barbiturates*, *papaverin*, *codeine* or *ethylene glycol* and others. A further example of such hyperadditive rise in poison effect is given by the *combination of cyanamid with alcohol.* A combination of poisons can become very dangerous in gas poisoning at the instance of an explosion. A classical example of this fact is the *combined gas poisoning with CO and nitrous gases* as it occurred in the catastrophal explosion of an X-ray film collection in a great medical center in Cleveland, a number of years ago, when more than 200 lives were lost.

Just as important as the synergism of poisons is their *antagonism*, which may have different causes. First of all, there may be a direct chemical reaction between the two components as in *neutralizing of an acid or alkali poisoning*, or in the *calcium therapy of oxalic acid poisoning*, or in the detoxication of *soluble barium salts* through *sodium sulfate.* Here we find a *mutual antagonism.* Similar processes play also a role in *cyanhydrogen*-poisoning-therapy by means of *sodium thiosulfate* in which process the non-poisonous sulfocyan or rhodan is formed from prussic acid.

In most cases, however, it is not a question of direct chemical reaction between the two antagonists, but other processes are taking place which are partly still unknown; and these processes do not even start at the same point of attack, but they influence in manifold ways the mutual solution- and distribution-relations in the cells. They exercise their antagonistic effect partly through displacement, partly by increasing or diminishing the excitability of the nervous elements. In such event, we speak of *pseudoantagonism.* Thus, the treatment of the *CO poisoning by* O_2 is based upon the mutual displacement in the hemoglobin combination. And again, other processes may play their part in the waking-effect of *calcium salts in magnesium narcosis*, or in the antagonistic influence of *atropine* on the *respiratory centre* paralyzed by *morphine.*

Of great practical importance is the *antagonism produced by convulsive poisons* in the therapy of poisoning with *sleep-producing poisons*, foremost, barbiturates and alcohol. But here, it seems that a selectivity of the antagonizing effect is of importance according to the point of attack of the

two poisons. Regarding *strychnine* and *picrotoxin*, for instance, which have similar points of attack as convulsive poisons, the latter shows better effect in the treatment of *barbiturate poisoning* (7); *cardiazol* (8) with its main point of attack in the brain stem, is a suitable antidote against brain stem hypnotics of the barbiturate group, while in poisoning with *chloral*, *urethan*, or *paraldehyde* which must be considered as cortex hypnotics, *cardiazol* and also *coramin* will have a less favorable effect. A further example of pseudo-antagonism is the very well known *curare-physostigmine antagonism* which seems to be the result of a series of complex chemical reactions.

This short survey of general toxicology may serve as an introduction to the special chapters which are to follow and in which I shall have occasion to return to some facts which I have so far only touched upon.

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RADIOLOGY AND RADIOTHERAPY COMBINED CONFERENCES

MARCY L. SUSSMAN, M.D., *presiding*

January 4, 1940

(*Cases Presented from The Department of Radiology*)

Parathyroid Adenomas with Osteitis Fibrosa Cystica

(*From The Medical Service of Dr. George Baehr*)

History (Adm. 448388). The patient, a 43 year old white male, was admitted to the hospital on June 21, 1938. In 1933, he experienced severe dysuria for about a week which was relieved by the cystoscopic removal of a calculus from the bladder. Since then, he noted increasing fatigue, weakness and lassitude. In 1935, an epulis was removed from the left mandible. This recurred in 1936 and was again removed. Two months prior to admission, the tumor reappeared. For the previous few months he noted "bone" pains involving the arms and legs.

Examination. There was a soft tumor mass of the left mandible between the canine and the first molar teeth, covered by mucosa which presented several bluish discolored and ulcerated areas. The blood pressure was 130 systolic and 80 diastolic. Examination of the heart and lungs revealed no abnormalities. The skin showed several small scattered pigmented nevi and pedunculated fibromata.

Laboratory data. The blood hemoglobin was 72 per cent. The blood Wassermann reaction was negative. The white blood cell count was 7900, with a normal differential count. The urine contained a trace of albumin and an occasional white blood cell. Roentgenograms of the bones showed generalized osteoporosis with cyst formation. The blood serum calcium was 14.0, the blood phosphorus 3.3, the blood urea nitrogen 29.0, and the blood sugar 90 mg. per cent. On a diet of approximately 100 mg. of calcium per day, 902 mg. of calcium in 4700 c.c. of urine were excreted in three days.

Course. On June 30, 1938, exploration of the neck revealed four large parathyroid masses. An adenomatous parathyroid gland was removed from region of the right inferior pole of the thyroid gland and another from the left superior pole region. The pathological report was "chief cell adenoma of parathyroid." Post-operatively, the patient was given parathyroid extract and calcium gluconate intravenously, and made an uneventful convalescence. Examination of the larynx post-operatively revealed evidence of a left recurrent paralysis. The blood serum calcium fell gradually and on July 9, 1938, was 11.4 mg. per cent, and the blood phosphorus 3.6 mg. per cent. The blood phosphatase had dropped from 49.5 to 33.0 King-Armstrong units. The patient was discharged July 10, 1938, to the Follow-up Clinic.

Interval history. He remained well symptomatically except for moderate urinary frequency during the day. In February 1939, roentgenograms of the bones revealed changes consistent with the clinical diagnosis of hyperparathyroidism. There was

diffuse decalcification of the skeleton, cyst formation in both bones of each forearm, in the upper end of the left fibula, in the right tibia and in the right humerus. During the summer of 1939, he had a large epulis removed from the upper jaw.

Second admission. The patient was readmitted on October 12, 1939, with a history of increasing bone pain in the upper extremities, weakness, and pain in the upper jaw, where another epulis had appeared.

Examination. This revealed no new findings beyond the epulis. The blood pressure was 142 systolic and 88 diastolic.

Laboratory data. The blood serum calcium had risen to 13.1 mg. per cent. The blood phosphorus was 3.1, the blood urea nitrogen 13.0 mg. per cent, serum albumin 4.9, and serum globulin 1.3 grams per cent. Blood phosphatase was 48.0 King-Arm-

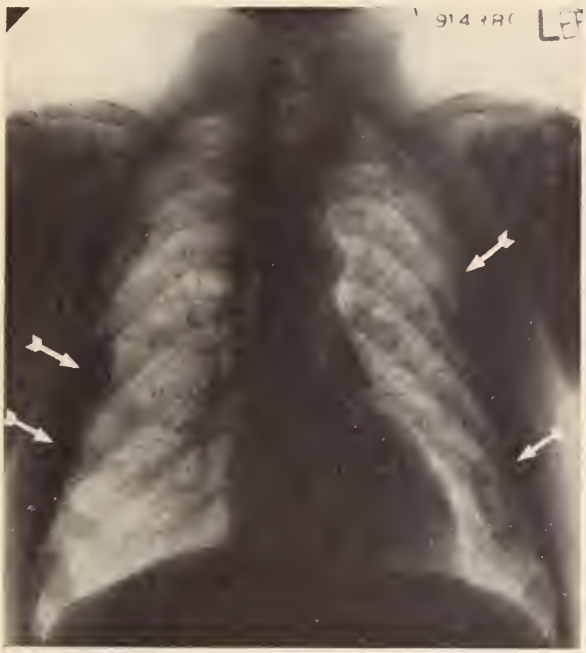

FIG. 1. Case 1. Expansion of the ribs by cystic swellings. There are similar changes in the clavicles and humeri.

strong units. The patient excreted 139.0 mg. of calcium daily on a diet of about 100 mg. of calcium per day.

Course. On October 28, 1939, a second exploration of the neck was performed. Masses of presumably adenomatous parathyroid tissue were removed completely from the region of the right upper pole of the thyroid gland and similar tissue was resected in the region of the left lower pole. Two slivers of the left tumor were implanted in the left sternomastoid muscle, on the supposition that if need for parathyroid tissue was present, the graft would take and function as normal parathyroid tissue. The resected tissue showed "two parathyroids, one strikingly enlarged, showing diffuse hyperplasia of chief cell types." Post-operatively, the patient was given parathormone and calcium in decreasing doses with no signs of tetany or parathyroid deficiency. At the time of his discharge on November 3, 1939, his blood calcium was 9.5, and the phosphorus 4.1 mg. per cent. Roentgenograms of

the skeleton revealed no changes other than those noted in previous examinations.

Third admission. The patient entered the hospital again four days later, on November 11, 1939. For the past day, he had noted marked tingling and quivering of his extremities and face to such an extent that he was forced to discontinue his work.

Examination. The deep reflexes were markedly hyperactive but equal with unsustained right pectoral and ankle clonus and left patella and ankle clonus. The Chvostek sign was positive; the Trousseau sign was negative. The blood pressure was 120 systolic and 80 diastolic.

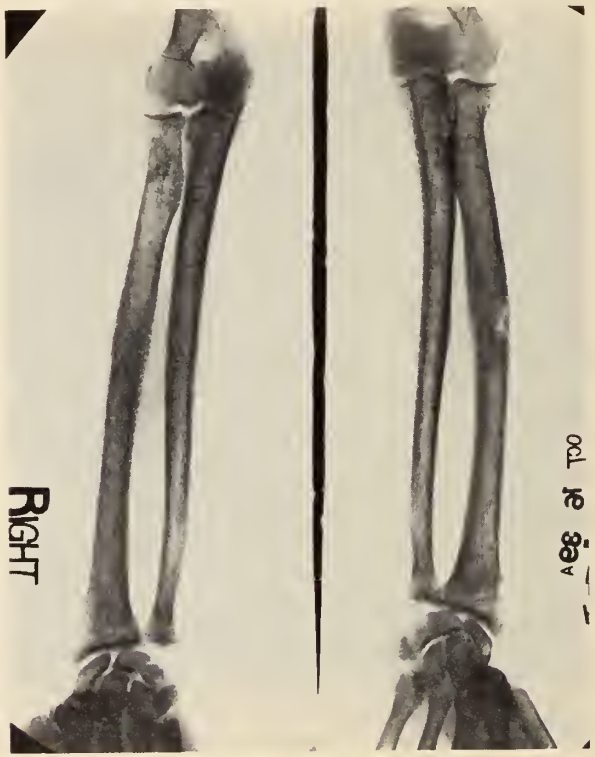

FIG. 2. Case 1. Bones of the forearms show similar cystic changes. There is unusual sclerosis about their peripheries. There is moderate decalcification of the entire bone.

Laboratory data. The blood serum calcium was 5.6 and the phosphorous 4.8 mg. per cent.

Course. The admission diagnosis was hypoparathyroid tetany. Treatment consisted of the intravenous injection of calcium gluconate and parathyroid hormone, and a low phosphorous diet with viosterol. The patient improved on this regime and after four days the blood calcium was 8.3 mg. per cent, and the blood phosphorus 3.6 mg. per cent. The Chvostek sign was elicited with difficulty. The blood carbon dioxide combining power was found to be 38.8 volumes per cent; this was attributed to the calcium chloride administered to a patient with chronic renal insufficiency. The carbon dioxide power rose to a normal level when the calcium chloride was

stopped. Six days after admission, he was placed on dihydrotachysterol therapy and the viosterol was discontinued. No change in the clinical condition was noted, except that the epulis diminished greatly in size after the operation. The patient gained ten pounds during this admission, and when he was discharged, on November 26, 1939, his blood calcium was 7.1 mg. per cent.

Comment: Dr. M. L. Sussman. Roentgenograms of the skeleton showed cyst formation in practically all the bones examined. The cysts were small in size and showed moderate sclerosis about their peripheries. The cysts were particularly marked in the ribs. There was a moderate miliary decalcification of the skull. The case is of particular interest because apparently multiple parathyroid adenoma were found. The case could be classified also as diffuse primary hyperplasia with hyperparathyroidism.

Parathyroid Tumor with Radiographic Changes Suggesting Paget's Disease

(From The Medical Service of Dr. George Baehr)

History (Adm. 431741). The patient, a 40-year old white female, was admitted to the hospital on February 9, 1932. The patient had had an appendectomy and cholecystectomy in 1927. She had borne two children both of whom are living and well. Since the birth of her last child in 1930, she had been troubled with incontinence of urine on straining, frequency and right loin pain.

Examination. The patient appeared well nourished and well developed. A systolic murmur was heard over the entire precordium. The blood pressure was 122 systolic and 80 diastolic.

Laboratory data. The blood hemoglobin, cytology and serology showed no abnormalities. A diagnosis was made of urethro-cysto-rectocele with incontinence of urine.

Course. An anterior and posterior colporrhaphy and sphincter repair were performed and the patient was discharged as improved. As the result of routine cystography, it was noted that the head and neck of the right femur had an unusual bone structure.

Second admission. In September 1932, the patient was re-admitted with a history of sharp epigastric pain radiating to the back, and a loss of 40 pounds during the intervening months. Physical examination was negative except for tenderness in the left upper quadrant. The blood pressure now was 158 systolic and 94 diastolic.

Laboratory data. The urine was normal. The basal metabolic rate was plus 8. The blood urea nitrogen was 11 mg. per cent. Urine cultures were negative as were X-ray examinations of the spine, and of the gastro-intestinal tract.

Course. On October 7, 1932 an exploration of the upper abdomen was done because of persistent right upper quadrant pain and tenderness. In view of the presence of enlarged lymph nodes in the vicinity of the common duct, presumably as the result of infection in the biliary tract, a choledochostomy was performed. On October 22, 1932, the patient was discharged to be followed in the Follow-Up clinic.

Third admission. In January 1934, incontinence recurred and the patient was re-admitted to the hospital. Because of the X-ray changes in the head and neck of the right femur, hyperparathyroidism was suspected.

Laboratory data. The blood calcium was 12.3 mg. per cent, the blood phosphorus 2.9 mg. per cent; the blood phosphatase 70 King-Armstrong units. A vaginal plastic repair for urinary incontinence was again performed with good results.

Interval history. Chemical studies of the blood performed at intervals revealed that the blood calcium varied from 11.9 to 13.8 mg. per cent, and the blood phosphorus from 3.0 to 3.3 mg. per cent.

Fourth admission. On October 9, 1934, the patient again entered the hospital. About three weeks prior to this admission, she was awakened from sleep by a severe pressing sensation in the right epigastrium radiating along the costal margin to the spine. There had been six attacks in this interval. On October 6, 1934, she fell.

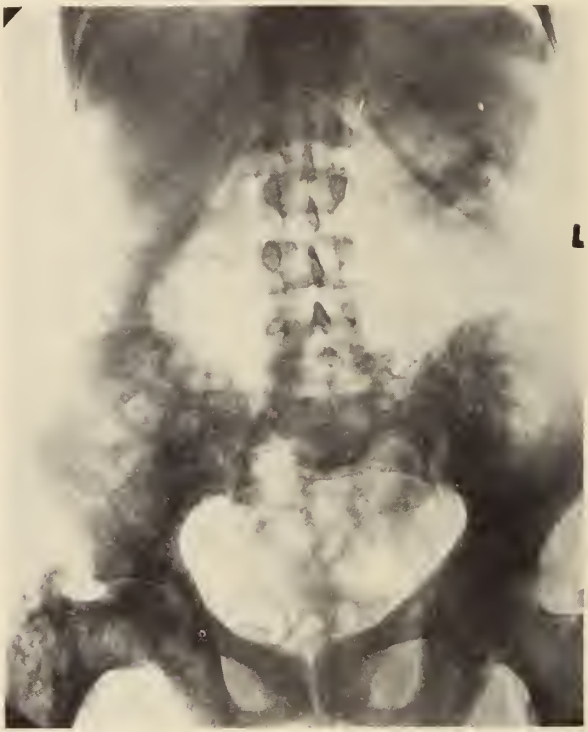

FIG. 3. Case 2. Both ossa innominata and the right femur show an increase in density of the bone and a general coarsening of the trabecular structure. The bone cortices are thickened.

Since then, the toes and sole of her left foot had been numb and she had pain in the left calf. Her last menstrual period occurred on August 22, 1934.

Examination. There was an area of hyperalgesia on the left side of the trunk from the level of the seventh to the tenth dorsal segments, which corresponded to the distribution of her pain.

Laboratory data. Ascheim-Zondek test was negative. The cerebrospinal fluid manometrics, cytology and Pandy test were not abnormal. X-ray examination showed compression of the third, fifth and eleventh dorsal vertebrae. The mandible was thickened and irregularly mottled. The skull, pelvis and long bones showed changes which were suggestive of Paget's disease. During the months of October

and November 1934, the blood serum calcium determination ranged from 12.2 to 14.5 mg. per cent and the blood serum phosphorus varied between 1.6 and 3.0 mg. per cent. The blood urea nitrogen was 10 mg. per cent.

Course. Paravertebral block anesthesia from the eighth to the eleventh dorsal vertebral segments, and a spinal brace relieved the symptoms incompletely.

Fifth admission. Urinary incontinence recurred in January 1935 and the patient was re-admitted on February 8, 1935 with the additional complaint of urinary frequency.

Laboratory data. The blood serum calcium was 11.8 and blood phosphorus 3.0 mg. per cent. The hemoglobin was 78 per cent and the white cell count was 8100.

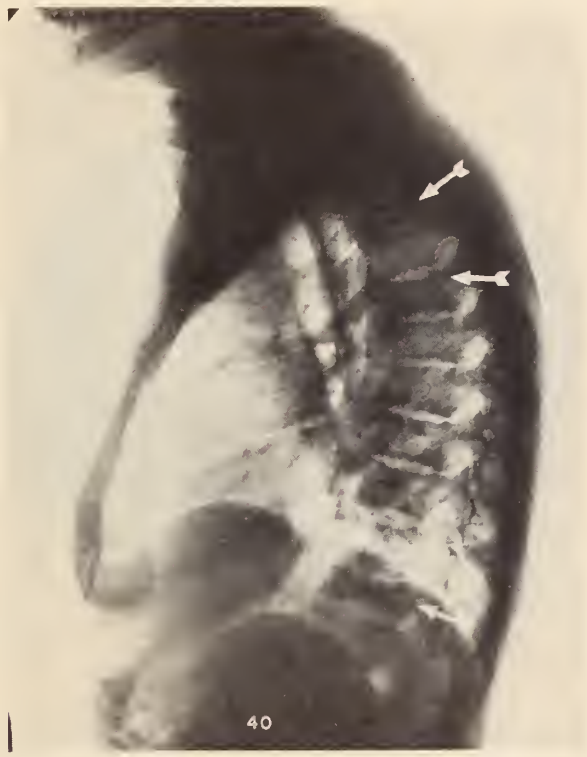

FIG. 4. Case 2. Compression of 3rd, 5th, 11th dorsal vertebrae with evidence of considerable sclerosis in these bodies.

The patient excreted 350 mg. of calcium daily on a diet which included about 375 mg. of calcium daily.

Course. Medical treatment ameliorated the urinary symptoms. However, the radicular symptoms persisted with varying degrees of severity.

Sixth admission. The patient was again admitted on January 21, 1936 in an attempt to obtain relief for the radiculitis.

Laboratory data. Blood calcium at this time was 12.5 mg. per cent; phosphorus 3.3 mg. per cent; phosphatase 134.0 King-Armstrong units; urea nitrogen 10.0 mg. per cent; total protein 5.3 mg. per cent; serum globulin 1.4 grams per cent; cholesterol 210 mg. per cent; sugar 100 mg. per cent; and chlorides 605 mg. per cent.

Course. On February 11, 1936, a biopsy of the greater trochanter of the right femur was performed and pathological examination revealed what was described as "osteitis fibrosa." Seven days later, an exploration of the neck was performed. No parathyroid glands were identified other than one small one on the right side near the lower pole of the thyroid gland, and this was removed. Pathological report was "parathyroid with frequent acinar formation but no other significant findings. Particles of thyroid without changes." Roentgenograms showed no change in the bones except that the skull appeared larger and that the bones of the calvarium were thicker. The patient was discharged on March 4, 1936.

Seventh admission. The patient was re-admitted on November 3, 1938. During the interval, she had lost thirty pounds in weight and three and a half inches in height. She received no therapy except for a high calcium diet and occasional analgesics. In October 1938, she developed a sensation of epigastric pressure not related

FIG. 5. Case 2. Thickening of the calvarium. Areas of increased density alternating with areas of diminished density with the "cotton-wool" effect of Paget's disease.

to meals. A week prior to this admission she passed a large stool which was black and since then her stools had been dark and tarry. Examination revealed the emaciation and loss in height indicated by the preceding figures. The blood pressure was 118 systolic and 76 diastolic.

Laboratory data. The blood calcium was 12.0; phosphorus, 2.9 mg. per cent; phosphatase 140.0 King-Armstrong units per 100 cubic centimeters; blood cholesterol 205 mg. per cent; blood sugar 100.0 mg. per cent; albumin 4.4 and globulin 2.1 grams per cent. Total protein was 6.5 grams per cent. Two calcium balance studies showed that with an intake of 275 and 238 mg. of calcium daily, the patient excreted 590 and 270 mg. per day respectively. Blood hemoglobin was 70 per cent, white blood cells were 5,000. The stool showed a one plus reaction to the guaic test. Gastric analysis showed that the free and total acid were within normal limits; the urine was normal. X-ray examination of the gastro-intestinal tract revealed no abnormality. The X-ray examination of the long bones showed no changes from those of the previous studies except for an increase in the compression of the twelfth dorsal vertebra and a marked bowing of the left humerus.

Course. In the hospital, the attacks of epigastric pain continued, as did the radicular pains. Paravertebral block anesthesia, opiates and a spinal brace offered slight relief. Because of the general condition of the patient, no mediastinal exploration was performed.

A note on the follow-up chart dated October 9, 1939 states: "Since discharge from hospital, patient has been to another hospital where a parathyroid adenoma was found and removed." Her blood calcium at this time was 9.1 mg. per cent, phosphorus 3.9 mg. per cent and phosphatase 30 King-Armstrong units. She was gaining weight and was free from pain.

Comment. Dr. M. L. Sussman. The roentgen findings in this case were typical of Paget's disease of the bone. There was marked thickening of the bones of the calvarium with irregular areas of sclerosis and ossification. The pelvic bones and the right femur showed widening of the trabecular structure with a pattern suggesting marrow fibrosis. The cortices were thickened. The vertebral bodies showed similar changes; several bodies were compressed.

On the other hand, the blood chemical studies and calcium balance studies were typical of hyperparathyroidism, finally confirmed by the removal of a parathyroid adenoma surgically. There can be little doubt that this patient suffers from two diseases which in all probability are coincidental.

Comment. Dr. A. B. Gutman. One rarely has the opportunity to see as many cases of hyperparathyroidism as were presented this evening. My discussion will be limited to one aspect of the subject: patients presenting features of both hyperparathyroidism and Paget's disease.

It is now generally accepted that hyperparathyroidism and osteitis deformans are different and unrelated diseases. The evidence for this view is summarized in this table which contrasts the clinical, chemical, and X-ray findings in 150 cases of hyperparathyroidism (from the literature) with the findings in 147 cases of Paget's disease (from the Presbyterian Hospital records). Hyperparathyroidism is rare, Paget's disease is not uncommon. Hyperparathyroidism occurs much more frequently in females than in males; in Paget's disease the sexes are equally involved. The symptoms and signs of hyperparathyroidism differ in many significant respects from those of Paget's disease, as indicated in the table. Hypercalcemia and hypophosphatemia are the rule in hyperparathyroidism, except when there is nitrogen retention due to impaired renal function; in Paget's disease, serum calcium and inorganic phosphorus values are within normal limits. Patients with hyperparathyroidism are usually in negative calcium balance; those with Paget's disease show normal calcium balance. Parathyroid tumors are not found in Paget's disease and the pathological changes in the bones in these two conditions are fundamentally different. In short, there is convincing evidence that these two conditions are discrete and unrelated entities.

The roentgenographic appearance of the skeleton in advanced hyper-

parathyroidism is characterized by generalized decalcification, often associated with cyst-like areas and with a finely granular mottling of the skull. The roentgenologist ordinarily has no difficulty in distinguishing this picture from the coarsely trabeculated bone structure, the sclerotic areas and the cotton-wool appearance of the skull in Paget's disease. But, as we now know, patients with hyperparathyroidism may show (in association with general decalcification and cysts) areas of marked *thickening* of bone, particularly in the skull and pelvis. Some slides shown illustrate such a case. Generalized skeletal decalcification is present and a large cyst occupies the proximal third of the tibia. There is, however, an extensive osteosclerotic area in the pelvis, as seen in these roentgenograms taken in 1932. In 1935, the condensation of bone in the pelvis had become so striking as to suggest the diagnosis of Paget's disease at that time (we would not consider this to be Paget's disease now). But chemical studies of the blood gave results typical of hyperparathyroidism and exploration in 1936 revealed a large parathyroid adenoma.

Let me describe a case in my own experience. A patient whose marked anterior bowing of the tibia, large head, kyphosis, strongly suggested Paget's disease. Roentgenograms of the tibia showed the characteristic features of advanced Paget involvement. The skull presented a coarsely mottled appearance consistent with Paget's disease; though not incompatible with hyperparathyroidism, in which the mottling of the skull may be so coarse, occasionally, as to simulate Paget's disease. There was no striking generalized skeletal decalcification, no cysts were present. These X-ray findings were (and are now) considered to be typical of Paget's disease. The blood and mineral balance studies indicated hyperparathyroidism, however, and exploration disclosed a typical parathyroid adenoma. A case shown here this evening likewise presented characteristic and even more widespread roentgenographic features of Paget's disease, yet proved to have a parathyroid tumor.

If, as seems clear, hyperparathyroidism and Paget's disease are unrelated entities, how can such co-existence of the two diseases be explained? I believe that most such cases described in the literature are, like my first case, not true Paget's disease associated with hyperparathyroidism but that the osteosclerotic areas may be healed osteitis fibrosa cystica, possibly the result of an earlier spontaneous remission of hyperparathyroidism. There are very few recorded instances of the co-existence of unequivocal Paget's disease and proved hyperparathyroidism, such as the case presented here this evening and my second case.

Reported by *N. Rudner, M.D.*

CLINICAL PATHOLOGICAL CONFERENCES

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

Wednesday, March 22, 1939

Myosarcoma of Stomach; Recurrence Nine Years after Gastrectomy; Survival of Twelve Years following Onset of Symptoms. Death Due to Carcinoma of Pancreas

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

History (Adm. 422633; P.M. 10788). *First Admission* (March 18 to May 4, 1929). The patient, a colored pianist, was first admitted to The Mount Sinai Hospital at the age of thirty-eight. Three years before (1926) he had had a hematemesis of about a glassful of bright red blood. The incident was preceded by nausea and a sense of faintness; it was followed by tarry stools. He was hospitalized at another institution. A gastro-intestinal series, taken at that time, was reported to reveal no pathology in the stomach. After receiving a transfusion he was discharged, without any definite diagnosis. He was well for two years. In 1928 he had another hematemesis, and was re-hospitalized at the same institution. This time the gastro-intestinal series revealed an oval, sharply defined filling defect in the stomach due to a mass arising in the anterior wall near the greater curvature. The regular contour of the shadow, the normal appearing rugae seen between it and the greater curvature, and the apparent flexibility of the gastric wall suggested the presence of a non-malignant tumor which had ulcerated. The films of the previous admission were reviewed and a small oval shadow, previously overlooked, was now apparent. Operation was advised. The patient refused and left the hospital against advice. In the ensuing year he was symptom-free except for a gradual swelling of the abdomen which was becoming very marked. He was then admitted to this hospital.

Examination. There was a huge, tense mass filling the epigastrium, the umbilical region, the hypogastrium, and encroaching upon the right and left hypochondriac regions. A fluid wave was demonstrated in the mass. Liver and spleen were not felt. There was no free fluid in the abdominal cavity. The heart appeared to be displaced upwards and to the left.

Laboratory data. Hemoglobin, 40 per cent; red blood cells, 2,450,000; white blood cells, 5,200 with a normal differential count. Repeated examinations of the stool were always guaiac negative. A Rehfuss test meal showed the presence of free hydrochloric acid. No blood was present in any of the specimens. A gastro-intestinal series showed, in addition to a large mass involving almost the entire

abdomen, an irregularly circular defect in the body of the stomach. The filling defect was indicative of the presence of a mass in the stomach, and suggestive of a gastric polyp. Malignancy could not be ruled out. A barium enema demonstrated the centrifugal displacement of the entire colon, hugging the lateral walls and the diaphragm.

Course. Following a transfusion the patient underwent an operation. On opening the peritoneum, a huge cystic mass presented in the midline. Upon incising this, a gush of fluid blood escaped; about three quarts were evacuated. Inspection now revealed a deep purple, flabby tumor mass apparently arising from the greater curvature of the stomach. A partial gastrectomy was performed. Recovery was uneventful and the patient was discharged seventeen days postoperatively.

The operative specimen consisted of a resected stomach and a tumor mass the size of a man's head. The tumor, which arose from the greater curvature of the stomach, protruded into the gastric lumen. There were on its surface many superficial ulcerations. Probing of these showed a direct communication through the stomach wall into a large cystic tumor. Thus, the neoplasm was both intra- and extra-gastric; the intra-gastric portion was solid, whereas the extra-gastric portion was cystic. Histologically, the appearance was that of a sarcoma, probably myosarcoma, although it could not, with certainty, be differentiated from a neurofibrosarcoma.

Interval history. The patient was carefully observed at frequent intervals in the Out-Patient Department. Over a period of the next five years he did very well. His general health was excellent, he was able to work, he gained twenty pounds in weight, and was completely free of any gastric symptomatology. In 1934 a mass was palpated in the region of the liver, probably in the retroperitoneal space. X-ray examination of the chest at that time revealed no evidences of any intra-thoracic metastases. He was given large doses of radiotherapy up to the limit of skin tolerance. The mass in the right upper quadrant gradually disappeared. He lost about ten pounds in weight. A blood count now showed a hemoglobin of 50 per cent, a red cell count of 3,350,000 and a white cell count of 3,000. There were no complaints offered by the patient. After radiotherapy was discontinued (1935) there was a gradual increase in the size of the abdominal mass. It was felt, however, that further irradiation at this time was inadvisable. Although he continued to lose weight, there were still no symptoms referable to the gastro-intestinal tract. A non-productive cough was now present; there was no chest pain. X-ray examination of the chest (December 1937) showed a small pleural effusion at the left base.

Second admission (April 13, 1938). During the entire interval period the patient had continued his normal occupation and activities. Six weeks before this admission he noted the progressive development of the icterus of the sclerae and skin. The stools had become light and the urine, dark. Pruritus was not present; appetite was good; there were no abdominal complaints. He had noted progressive, painless enlargement of the abdomen. Cough, noted in 1937, was still present, but unaccompanied by any hemoptysis or blood-streaked sputum. There was progressive, though only moderate weakness. In the two months before readmission, he lost an additional fifteen pounds.

Examination. The patient appeared poorly nourished, chronically ill, and highly icteric. Several discrete lymph nodes were palpable in the left axilla and both groins. The heart was enlarged downwards and to the left. A heaving apical pulsation was both visible and palpable; extrasystoles were present. Blood pressure was 190 systolic and 110 diastolic. Lungs were normal to examination. The abdomen was protuberant. The skin overlying the umbilical area was deeply pigmented and indurated, the result of previous radiotherapy. There was bulging of the flanks. A definite fluid wave was elicited. The ascites obscured all the vis-

cera and any possible mass. The prostate was enlarged. The skin and sclerae were ieterie. Slight elubbing of the fingers was present.

Laboratory data. Hemoglobin, 56 per cent; red blood eells, 3,700,000; white blood eells, 8,100. Differential eount was normal exeept for an eosinophilia of 9 per eent and a basophilia of 2 per cent. Blood Wassermann test was negative. Blood sugar, 85; urea nitrogen, 9; bilirubin, 9; eholesterol, 500; ester, 125; icterus index, 35. Urine showed a traee of albumin, 2 plus bile and urobilin positive in a 1 to 2 dilution. Galaetose tolerance test and sodium benzoate tests of the liver funetion were normal. Chest x-ray examination showed a moderate enlargement of the left ventriele; there was no evidenee of a metastatie lesion. A gastro-intestinal series showed a subtotal gastrie reseetion; there was no definite evidenee of reeurrence; the stoma was wide. An electrocardiogram showed left ventrieular preponderanee and evidenees of involvement of the ventrieular musculature. An abdominal puneture yielded elear yellow fluid with a specifie gravity of 1.008 and total protein of 350 mg. No tumor cells were found.

Course. The clinieal diagnoses were: reeurrent myosarcoma of the stomaeh with obstruetion of the common duet and portal vein with aseites and jaundiee; hypertensive and arterioselerotie heart disease. Because of the previous exposure to heavy irradiation, further radiotherapy was felt to be eontra-indicated. Mereurial diureties were ineffeetual in diminishing the aseites. Beeause he eontinued to be essentially asymptomatic, he was diseharged to be followed in the elinie. On the morning after discharge he suddenly eomplained of weakness, and he fainted. An ambulanee surgeon was ealled, and found him dead. Thus, he died twelve years after the appearanee of the first symptoms, and nine years after his gastrectomy.

Necroscopy findings. The *stomach* was normal with no evidenee of any reeurrence. Lying between the aorta and inferior vena cava, at the level of the duodenum, was a large, bulging, retroperitoneal tumor mass. On section, there were many fibrous whorls not unlike a uterine fibromyoma. This mass represented a metastases from the original gastric neoplasm. The head of the *pancreas* was the site of a malignaney in the nature of a panereatie careinoma. It eompressed the portal vein and the eommon duet, resulting in marked dilatation of the latter. A pseudoeyst was present in the spleen. The *heart* was enlarged and showed diffuse fibrosis of the myocardium.

Comment. Dr. A. A. Berg. I have performed this operation on many other similar cases. It is my impression that, clinically, this type of tumor is essentially non-malignant. A wide removal is usually followed by freedom from recurrence for many years. I can cite cases that went for five years after gastrectomy without recurrence.

Dr. Winkelstein. The four diagnostic criteria for this type of neoplasm are: 1) A roentgenographic picture of a circular defect in the stomach with an intact outline; 2) the presence of gastric acidity; 3) gastric hemorrhages; and 4) the presence of an extragastric mass. These permitted the correct pre-operative diagnosis in this case.

Dr. Klemperer. I wish to present the statistics on the relative frequency of this type of tumor. In the past twenty years, seventeen sarcomas of the stomach have been encountered in a total of six hundred and fourteen gastric tumors of all descriptions. This is an incidence of about 2.8 per cent. Of these seventeen, more than one-third were lymphosarcoma. The follow-up analyses bear out Dr. Berg's impression, namely, that

sarcomas of the type presented are not very malignant. Thus one-third of all the sarcoma cases were well after four years.

Dr. Baehr. I attribute the enormous size of the extragastric portion of the tumor to probable cystic degeneration. The coincidental association of the pancreatic neoplasm, which was the actual cause of death, should be pointed out. Death was due to this new malignant disease, not to the late recurrence of the neoplasm of the stomach.

Wednesday, March 29, 1939

Carcinoma of Apex of Lung with Involvement of Sympathetic Nerve. Compression of Mediastinal Vessels and Thoracic Duct with Chylous Pleural Effusion

(*From the Medical Service of Dr. George Baehr*)

History (Adm. 432849; P.M. 11049). This was the first admission of a forty-five year old white male who was well until the onset of the present illness, five months before admission. At that time he began to have pain in the right upper chest posteriorly, above the scapula. The pain was sharp and intermittent at the onset, but soon became constant with nocturnal exacerbation. One week following the onset of the pain, he developed a dry, non-productive cough. This occurred in paroxysms and appeared to be initiated by a tickle in the right side of the throat. There was never any production of sputum. Dull, right frontal headaches occurred every three to four days. The patient was treated for neuritis and was given capsules which relieved the pain. However, over a period of three and a half months the pain steadily became more intense; the cough was unchanged. On the advice of his physician, he now had seventeen teeth removed. Several days later (i.e. 6 weeks before admission) he noted slight swelling of the right side of his face and slight narrowing of the right palpebral fissure. The pain now shifted to the right shoulder and gradually spread down the arm to the elbow. At the same time, the patient experienced numbness of the little finger and ulnar half of the ring finger extending along the hypothenar eminence to the wrist. Whenever the shoulder pain became intense, these two fingers would become hot and flushed. During the five weeks before admission the pain remained fairly constant, being excruciating at night. During the week before admission, his hand became weak; no paralysis was present. Two areas on the inner side of the right arm, just above the elbow and just above the axilla, were frequently sore.

Two weeks before admission he observed for the first time that the right side of his face and the right axilla would be dry, while he would be perspiring on the left side. Enlarged veins on the right side of the chest

were also noted at this time. One day before admission, there was rather sudden and marked swelling of the right side of the face and neck, which persisted. There was very little loss of weight. Slight dyspnea, chiefly at night, and some increased difficulty in respiration were present.

Examination: He was a well developed, well nourished man with marked puffiness of the face and eyelids; there was swelling of the neck from the supraclavicular area extending upwards bilaterally. The color of the skin of the face and neck was definitely cyanotic. The fleshy structures of the head and neck were out of proportion to the remainder of the body. Distended veins were present over the superior chest with evidence of marked collateral circulation over the chest, shoulders, back and abdomen. The veins filled from above downward. The right pupil was miotic and smaller than the left. The right palpebral fissure was narrowed, and slight exophthalmos was present on that side. The disc margins were blurred. The trachea was in the midline and fixed so that there was only slight lateral or up-and-down motion. Shotty nodes were felt in both axillae, but were more marked on the left. Tenderness was elicited over the right anterior superior chest, including the supraclavicular area, extending down to the third rib and into the axilla. Retromanubrial dulness was increased. Dulness was present over the left upper lobe. The right diaphragm was elevated and limited in motion. The heart was normal. The right pulse was weaker than the left. Blood pressure on the right was 105 systolic and 80 diastolic and on the left 130 systolic and 70 diastolic. Moderate clubbing and cyanosis of the fingers was noted. Neurologically, in addition to the Horner's syndrome there was a peripheral hypesthesia over the distribution of the right ulnar nerve extending down the medial aspect of the hand, and the fourth and fifth fingers; there was a relative weakness of the muscles on the right as compared with those on the left; an absence of sweating over the right side of the face and neck was observed. The impression was that of a neoplasm at the right pulmonary apex. Mediastinal metastases with venous obstruction. Right Horner's syndrome. Right phrenic paralysis.

Laboratory data. Hemoglobin, 92 per cent; white blood cells, 10,600 (85 per cent polymorphonuclear leucocytes, 7 per cent lymphocytes, and 8 per cent monocytes). Sedimentation time was 28 minutes. Urine was negative except for a very faint trace of albumin. Blood chemistry showed a urea nitrogen of 12; sugar, 100; total protein, 5.6. Venous pressure was 36 cm. Saccharine time was 24 seconds. Biopsy of a lymph node showed a "fatty lymph node with hyperplasia of sinus endothelial cells." X-ray examination of the chest revealed a marked widening of the superior mediastinum which was interpreted by the roentgenologist as either Hodgkin's disease or lymphosarcoma. Also, there was a clouding of the apex of the right pulmonary field, interpreted as being the probable result of an extra-pleural spread of the mediastinal tumor. An effusion was present beneath the right lung.

Course. Radiotherapy was applied to the mediastinal tumor mass without delay. Evidences of increasing fluid at both bases became more marked. A chest aspiration on the left side yielded 2,000 cc. of turbid, chylous fluid with 5 white cells per cu. mm. No organisms were present; no tumor cells were found. However, chemical analysis revealed a total fat of 1205 mg. per cent; the protein was 2.9 gm. per cent. On smear, many large vacuolated cells were seen. A potain aspiration of the right chest yielded 1,700 cc. of turbid fluid with a fat content of only 114.5 mg. per cent; again, no tumor cells were found. It was felt that these findings pointed to an obstruction of the thoracic duct. At first, radiotherapy resulted in improvement. The edema of his face and neck diminished markedly and a repeated X-ray examination showed a marked diminution in the size of the superior mediastinal mass. However, he developed progressive swelling of both arms and the venous pressure remained elevated

to 32 cm. He became progressively more dyspneic, orthopneic, cyanotic, and developed increasing ankle edema. For a while the edema of his left arm disappeared but then recurred and became progressively worse. He became weaker, irrational, and disoriented, showing increasing evidence of respiratory difficulty, and died seven weeks after admission.

Necropsy findings. Dr. Klemperer. A tumor was found in the extreme apex of the upper lobe of the right *lung.* Although there was no other lung involvement, the tumor had extensively infiltrated and invaded the structures above and medial to the right upper lobe. Thus, it was found to be densely adherent to the neighboring bony structures. The vagus nerve, the brachial plexus and the sympathetic nerves were all involved in the callous, metastatic new growths. In the mediastinum, it was in intimate contact with many vessels, nerves and lymph nodes. In this latter situation, the superior vena cava, three inches above its entrance into the right auricle, had its lumen narrowed to probe size and was thrombosed; the innominate and subclavian veins, on both sides, were thrombosed. By direct extension, the first and second ribs on the right side and the fourth thoracic vertebra had become infiltrated by neoplastic tissue. Both *adrenal glands,* as well as both *kidneys,* were the sites of metastatic implants.

Comment. Dr. Klemperer: This is one instance of a group of cases characterized by a small, peripheral primary carcinoma of the lung, that is attended by a very early and extensive invasive tendency. In addition, the metastases characteristic of a bronchus carcinoma were also present, i.e. involvement of the adrenals and kidneys.

The unusual, and recognizable symptom complex was first emphasized by Pancoast. It is now known that most cases presenting the clinical features of this syndrome are due to an apicaly situated pulmonary neoplasm.

Dr. Baehr: Involvement of the sympathetic nerves with resultant Horner's syndrome is rare in Hodgkin's disease or lymphosarcoma. On the other hand, in carcinoma, symptoms referable to involvement of the sympathetic system, are not at all uncommon. This experience should have been evaluated in the differential diagnosis and both Hodgkin's disease and lymphosarcoma discarded in favor of a carcinoma extending from the apex of the lung.

Reported by *Max Ellenberg, M.D.*

CLINICAL NEUROPATHOLOGICAL CONFERENCE

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

Monday, October 9, 1939

*Case 2.** Granuloblastoma; Left Cerebellar Lobe

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

History (Adm. 434483; P.M. 11043). A boy, aged 12 years, was admitted to the hospital on January 6, 1939. At the age of six months he had had pneumonia and typhoid fever; he subsequently passed through the usual illnesses of childhood without any apparent sequelae. On December 3, 1938, while at play, he fell and struck his head. There was no immediate complaint but the following day he complained of a slight headache. For the next five days he was free of symptoms and attended school. Then he met with another accident; he was struck with a snowball over the right eye. The only apparent result of this was a skin bruise. Two days later he experienced severe headache in the back of his head and vomited. The headache and repeated vomiting continued for four days. He was taken to a hospital where he was found to be drowsy and apathetic and it was recorded that his left pupil was slightly larger than the right, the fundal veins were full, and a Kernig sign was present on both sides. Dysdiadochokinesis was observed on the left side. The cerebrospinal fluid was reported as normal in all phases. A subdural hematoma was suspected but none was found through bilateral trephine openings. The patient continued to vomit and his condition declined. Two weeks after operation a ventriculography was performed. It disclosed marked dilatation of the lateral and third ventricles. On the same day a suboccipital craniotomy was performed. Aspiration through the dura over the left cerebellum yielded a small amount of xanthochromic fluid mixed with blood and fragments of tissue. The tissue on microscopic examination, was reported as being neoplastic and probably of the "medulloblastoma" type. Following the operation, the patient seemed brighter. His vomiting ceased and he was fed by means of a Levin tube. A week after operation the patient was transferred to The Mount Sinai Hospital for X-ray therapy.

Examination. The boy was emaciated. Except for an occasional crying sound, he lay quietly in bed. He did not respond to questions or commands but stared vacantly ahead. Occasionally spontaneous movements would occur, usually in the right upper limb. There was little, if any, voluntary movement in the left upper

*Case 1 was reported in the previous issue of the Journal (Vol. 7, No. 2).

extremity. He held his lower extremities flexed and abducted. He made only feeble attempts to swallow liquids. His pupils were dilated and equal and they reacted to light. Both disc margins were blurred and the fundal veins were distended. There was a marked atrophy of all museles of the extremities and trunk. The left upper extremity was weaker than the right and displayed hypotonia of the finger and wrist joints. All of the deep reflexes were depressed. Plantar flexion was described as poor. There were no pathologieal reflexes. The abdominal reflexes

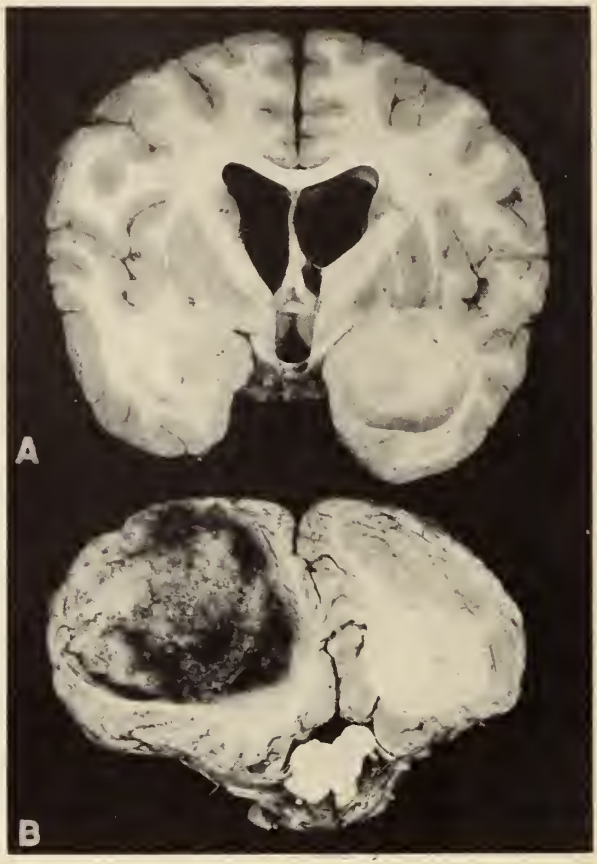

FIG. 4 (ease 2). A. A coronal seetion of the brain showing the marked internal hydrocephalus affecting the lateral and third ventricles.
B. The tumor oceupies almost the whole of the left cerebellar hemisphere.

were active on both sides. Pin-prick stimuli resulted in reflex muscle jerks. Both ear drums were perforated and there was blood in the right eanal.

Course. X-ray therapy was instituted. Ventricular taps were performed on the first two days of admission and yielded xanthochromic fluid. For a short while the patient seemed brighter. On the seeond day of his stay in the hospital his respirations suddenly slowed to fourteen a minute. He died three days later, on January 10, 1939, exactly one month after the onset of his headache and vomiting.

Necropsy findings. Brain. Gross. The cerebral hemispheres showed evidence of inereased intraeranial pressure. The left cerebellar hemisphere was softer and

larger than the right. Its dorsal surface had lost its normal markings. On its ventral surface there was a circular hemorrhagic area about 4 mm. in diameter, which corresponded to a perforation of the dura in this region.

On sectioning, marked internal hydrocephalus was found (fig. 4 A). It was bilaterally symmetrical and affected all the ventricular compartments except the fourth ventricle. This, in turn, was reduced in size and displaced toward the right. The left cerebellar hemisphere was found to be occupied for the most part by a

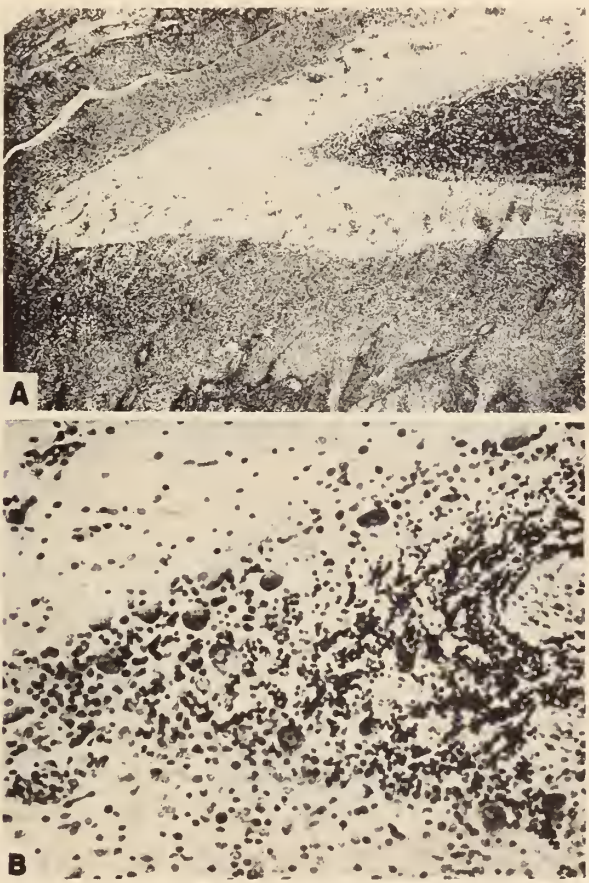

FIG. 5 (case 2). A. A section of the cerebellum showing the molecular layer outlined peripherally by tumor tissue. Tumor cells are also present in the molecular layer, denser toward the periphery, often about blood vessels (Nissl, 48×).

B. A higher magnification of *A* showing well-preserved and undisturbed Purkinje and granule cell layers in this region (310×).

large tumor mass (fig. 4 B). This measured 5 cm. in its longest diameter and extended to the surface of the cerebellar hemisphere where it became apparent through the thickened, discolored meninges overlying the dorsal aspect of the posterior lobe. The cut surface of the mass was grayish near the periphery, gradually becoming reddish toward the center.

Microscopic. The tumor was rich in cells and in blood vessels. Its structure was most clearly recognized in parts which were near well-preserved cerebellar cortex.

There the tumor cells, assuming a band formation, skirted the outer surface of the molecular layer and extended into the sulci alongside the pia which was infiltrated by, and fused with, the tumor tissue (fig. 5 A). The molecular layer in such regions also contained tumor cells, singly or in groups, usually in the proximity of blood vessels. Their greater concentration, however, was at the periphery of the molecular layer, leaving well-preserved Purkinje and granular cell layers undisturbed (fig. 5 B). This arrangement would suggest the probability that here the tumor cells were in the initial process of inward migration.

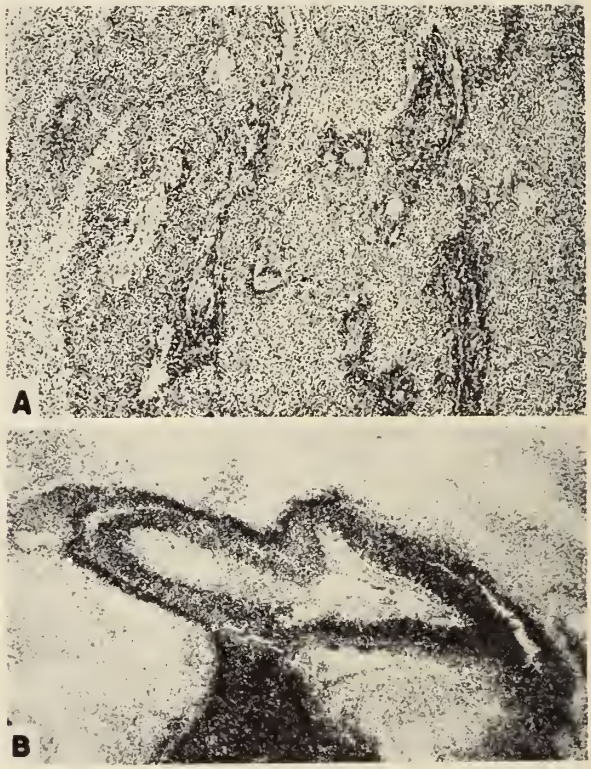

FIG. 6 (case 2). A. An area of tumor tissue showing mosaic patterning (Nissl, 100×).

B. A blood vessel within the tumor surrounded by tumor cells in layers of varying density simulating the pattern seen at the periphery of the fetal cerebellum (Nissl, 48×).

More centrally the tumor cell arrangement gave the appearance of a mosaic pattern (fig. 6 A), as though the tumor tissue consisted of somewhat irregular, but more or less individual units. Each such unit had in its center a vessel in cross or longitudinal section, each vessel usually being surrounded by a layer of densely packed cells which was in turn surrounded by a wider zone of less densely packed cells. In some regions three perivascular layers could be distinguished (fig. 6 B) producing an arrangement simulating the pattern seen in the developing cerebellum of a fetus. The cells in the most internal layer were large and were represented by large, round, fairly densely stained nuclei, there being practically no visible cytoplasm. In the next and more rarified zone the cells contained a less deeply stained

nucleus and often displayed a fair amount of cytoplasm. The latter, when visible, was elongated and irregular in outline. Among them there were some cells resembling the "granule" cells, differing from them in that they were larger and the nuclei were hyperchromatic. Multinucleated cells were occasionally encountered, in addition to unipolar cells with large vesicular nuclei. Throughout the various parts of the tumor there was an exceedingly large number of mitotic figures.

In a Bielschowsky preparation cells resembling unipolar and bipolar neuroblasts were noted. Sections stained by the Globus modification of the Hortega silver carbonate stain occasionally disclosed cells suggestive of bipolar spongioblasts.

Comment. Dr. Globus. The histological structure of the tumor resembles that of the so-called granuloblastoma reported by Stevenson and Echlin in 1934.[2] The arrangement of the cells in this type of tumor is more significant in the identification of the tumor than the individual cells. Stevenson and Echlin pointed out the tendency for this type of neoplasm to spare the outline of the foliae by proliferating most densely along their surfaces, separating rather than effacing them. In this case, however, there was much less sparing of the folia and much more marked invasion of the cerebellum, probably because of the more rapid growth, as evidenced by the marked abundance of mitotic figures and the preponderance of undifferentiated cells. Stevenson and Echlin pointed out that this type of growth duplicates the behavior of the external granular layer of fetal and early infant life. At about the third month of fetal life, according to the later studies of Kershman,[3] neuroepithelial cells at the posterior lip of the fourth ventricle migrate to the periphery and there proliferate to form a dense cellular nest. Cells from this nest migrate over the entire external surface of the fetal cerebellum producing a sheet of cells, the external granular layer. This zone of cells persists about to the end of the first year of postnatal life, gradually disappearing during the second six months. Until the fourth month of postnatal life, cells from this superficial layer migrate inwards giving rise to neuronal elements only. In the fourth month, cells of this superficial layer begin to produce elements which Kershman considered spongioblastic in nature, giving rise to special types of cerebellar astrocytes.

The presence in this tumor of spongioblastic elements, together with neuronal elements, is also evidence of the bipotential character of the wandering neuroepithelial cell which composes the external granular layer of the cerebellum in fetal and early infant life. The term granuloblastoma, suggested by Stevenson and Echlin, is useful since it indicates cells of a common type, their blastomatous nature, and their relation to the formation of the granule cell layers in the cerebellum.

Reported by *J. M. Zucker, M.D.*

[2] Stevenson, S., and Echlin, F.: Nature and origin of some tumors of the cerebellum—medulloblastoma. Arch. Neurol. & Psychiat., 31: 93, 1934.

[3] Kershman, K.: The medulloblast and the medulloblastoma—a study of human embryos. Arch. Neurol. & Psychiat., 40: 937, 1938.

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.

Non-Putrid Pulmonary Suppuration. M. L. Sussman. Am. J. Roent. & Rad. Ther. 40: 22, July 1938.

The following considerations of roentgenologic interest are emphasized. (*1*) In its early stages suppurative bronchopneumonia has no differentiating features from other forms of bronchopneumonia. In the mild cases resolution takes place promptly. The severer forms of the disease are not common except in epidemics but are more frequent than is usually suspected due to the fact that the complications are not always recognized at the time of the acute illness. (*2*) The irregular mottling that appears roentgenologically in the course of a bronchopneumonia may be due to the formation of numerous suppurative foci but may be due simply to an irregular resolution. Only the course of the disease permits their differentiation. Similarly, simple resolving lobar pneumonia simulates the irregular mottling produced by suppurative foci and cannot ordinarily be differentiated from it roentgenologically. (*3*) In spite of a very mild clinical course, repeated roentgen examinations may reveal abscess formation which may be solitary or multiple. The solitary non-putrid abscess, however, is uncommon. Usually cases of single lung abscess are putrid. (*4*) The presence of pulmonary cavitation is not incompatible with complete spontaneous resolution although recovery may be slow. The clinical condition of the patient is a much better guide to prognosis than the roentgen appearance. (*5*) The presence of an abscess is only surely indicated roentgenologically by a fluid level. The absence of a level, however, does not exclude an abscess; it may be filled with fluid at the time of examination. (*6*) Roentgen signs of atelectasis often appear relatively early in the disease and are then probably due to bronchial obstruction as a result of plugging by thick tenacious secretions. Persistence of the atelectasis is the result of shrinkage due to maintenance of this contracted state by an interstitial fibrosis. In these cases the affected lobe may appear homogeneously consolidated and so simulate lobar pneumonia. (*7*) Pleural involvement may take the form of simple effusion, general empyema, encapsulated empyema, encapsulated or general pyopneumothorax. The pathogenesis of these processes is not discussed beyond indicating that pyopneumothorax appears most often to be associated with a perforated lung abscess and bronchial fistula. (*8*) Loculated pyothorax, with or without a fluid level due to the presence of air, is common. Loculation may occur anywhere within the pleural cavity. Infrapulmonary and paramediastinal collections present most difficulty in diagnosis. The latter are usually demonstrated clearly in the lateral view but it is usually not possible to state whether the mediastinum is also involved. Parapericardial collections present the same difficulties.

Infrapulmonary collections must be suspected in suppurative bronchopneumonia when the diaphragm appears abnormally high. The shadows of the lower lobe pneumonia, infrapulmonary collection and diaphragm are apt to merge. Displacement of the heart to the opposite side suggests a fluid collection. Pneumoperitoneum may be necessary to establish the position of the diaphragm, although on the left the position of the gastric air bubble may give the same information. Exploratory aspiration and operation often have to be proceeded with in spite of inconclusive roentgen evidence (Touroff). (*9*) It is often not possible to state whether a cavity is pulmonary or pleural. Size and the amount of surrounding density are of no great practical value in the differentiation; the large cavities are often intrapulmonary while the small fluid levels may represent pleural loculations. Lateral and oblique views are of greatest value in localizing the process. If the shadow is due to a pleural collection there should be one position in which it is shown as a more or less semicircular shadow, base against the chest wall. Interlobar collections are also identified in oblique and lateral views. (*10*) Potain or diagnostic aspiration performed carefully should not permit the introduction of air into the pleural cavity. The presence of a fluid level, therefore, usually indicates a pulmonary cavity regardless of previous aspiration. (*11*) Even after adequate drainage of a pulmonary or pleural collection of pus, a similar bronchopneumonia may develop elsewhere in the lungs with its own set of complications. (*12*) Bronchial dilatation is a common accompaniment of the disease. It develops early but is not necessarily permanent. A cylindrical dilatation, for example, may be caused by paresis of the bronchial muscle. Bronchographic studies are of great value in recording the course of this complication. (*13*) The operative indication in suppurative bronchopneumonia is not discussed beyond recording the obvious conclusion that it should be based upon clinical as well as roentgen data. The roentgen finding of a fluid level, for example, is only part of these data. (*14*) The disease in children is essentially the same as in adults although usually more extensive. Obstructive emphysema and atelectasis are apt to be prominent features in infants. (*15*) A complete roentgen examination, including roentgenoscopy and roentgenography in sagittal, oblique and lateral views, is essential for the diagnosis and localization of pulmonary suppurative disease.

The Clinical Significance of Pancreatic Reflux. R. Colp and H. Doubilet. Ann. Surg. 108: 243, August 1938.

When the pancreatic duct empties into the common bile duct above the sphincter of Oddi, spasm of that muscle will convert the common and pancreatic ducts into a single continuous channel. Under these conditions pancreatic juice may be retrojected up the biliary tract. Seven cases of this nature are presented in which pancreatic enzymes were detected post-operatively in the bile draining from a choledochostomy tube. In six of these the presence of pancreatic reflux was further confirmed by the visualization of the pancreatic duct after the injection of lipiodol into the biliary tract. The retrojection of lipiodol into the pancreatic duct could be easily produced when spasm of the sphincter was present. The duct could not be filled with lipiodol when the tonicity of the sphincter was normal or low. In such cases morphine was given to produce spasm of the sphincter of Oddi. The biliary drainage was also examined fractionally during twenty-four hour periods and it was shown that the maximum concentration of pancreatic enzymes in the bile occurred after a heavy meal. During the night and early morning these enzymes might be totally absent. A reflux of the pancreatic juice into the common bile duct in these cases was apparently harmless and the post-operative course of patients was uneventful. However, another case was presented in which bile peritonitis was caused by reflux of pancreatic juice into the gallbladder. Reference was made to three cases of acute cholecystitis caused by pancreatic reflux.

Factors which Reduce Gastric Acidity. A Survey of the Problem. F. Hollander. Am. J. Dig. Dis. 5: 346, August 1938.

This review article discusses at length all the factors in the course of a gastric analysis which normally cooperate in lowering the gastric acidity from its initial high value of 160–170 mM (as in the parietal secretion) to 50 mM or lower. One of these factors, admixture of test meal with stomach contents, is extraneous and non-physiological, and a method has been described whereby in future investigation its influence can be corrected quantitatively. A second factor, variation in composition of the parietal secretion itself, finds little support today by reason of the evidence which has already been accumulated against it. The six remaining factors—admixture of saliva, regurgitated, intestinal contents, peptic secretion, a specific dilution secretion, mucous secretion, and reabsorption of HCl—are all possibilities which require painstaking investigation. Thus, this discussion is intended to serve as an analysis of the broad problem of acidity regulation, looking forward to a quantitative evaluation of these several factors. Basically the observed variations in gastric acidity are due to neutralization by buffer substances—protein, phosphate, and bicarbonate—and to dilution by the fluids, which contain them. But which these fluids are, and whether there is one which serves to a greater degree than any other in the capacity of buffer-containing secretion—these questions still remain to be investigated.

The Significance of the Conditions of Exposure in Study of Measles Prophylaxis. S. Karelitz. J. Pediat. 13: 195, August 1938.

Studies formerly published with Dr. Schick were extended. By accumulation of data of the results of various preparations used in the prophylaxis of measles under different conditions of exposure, it was shown that the incidence rate of measles and the ability to prevent measles with a given dose of serum, varied according to whether the exposure occurred in hospitals, in homes with good or poor hygienic conditions, in buses, schoolrooms, playgrounds, etc., in other words, under conditions of exposure which varied from the doubtful to intimate, and from a period less than six hours to one of four to eight days. The results indicated that intensity and duration of exposure are important factors in the evaluation of a measles prophylactic agent as well as in the determination of the secondary attack rate of the disease. These studies imply further that, as in bacterial disease, the dosage of measles virus is important, and further, that measles spreads primarily by direct contact and is airborne only to a limited extent.

Colorimetric Determination of Equilenin And Dihydrocquilenin. W. Marx and H. Sobotka. J. Biol. Chem. 124: 693, August 1938.

The female sex hormones, equilenin and dihydroequilenin, found in pregnant mares' urine, are closely related to estrone and estradiol. A method is described for their colorimetric estimation based on their coupling with diazotized p-nitrobenzene azodimethoxyaniline.

The Effects of Hydrogen Ion Concentration, Fatty Acids and Vitamin C on the Growth of Fungi. S. M. Peck and H. Rosenfeld. J. Invest. Derm. 1: 237, August 1938.

The effects of various hydrogen ion concentrations on the growth of Trichophyton Gypseum, Epidermophyton Inguinale and Monilia Albicans were studied. Trichophyton Gypseum was capable of producing a more alkaline pH in Sabouraud's bouillion when grown on a medium with an initial pH of 4.0 to 8.0. At an initial pH of 9.0 and 10.0 it acidified the medium.

The fungicidal effects of the fatty acid series beginning with formic acid with one

carbon atom and concluding with capric acid with 10 carbon atoms, as well as the unsaturated undecylenic acid, were studied.

Valeric acid with 5 carbon atoms in its chain seems to have had the greatest fungicidal properties of all the fatty acids studied. It seemed, however, that acids with an odd number of carbon atoms were more fungicidal than those with even numbers.

Vitamins A, B, and D did not affect the growth of the fungi. Cevitamic acid, however, has definite fungicidal and fungistatic properties which are not due primarily to the changes in the hydrogen ion concentration produced by the addition of this substance to the media.

The Mechanism of After-Contraction. M. R. Sapirstein, R. C. Herman and I. S. Wechsler. Arch. Neurol. & Psychiat. 40: 300, August 1938.

The authors investigated the phenomenon of after-contraction, as involuntary repetition of an originally intended movement, by means of pharmacologic, physiologic and clinical studies. They found that after-contraction is influenced by facilitation, fatigue, and duration of effort and by contraction of ipsilateral muscles. The phenomenon is found to be normal in patients with tabes and cerebellar disease, it is prolonged in paralysis agitans, and is diminished in disease of the pyramidal system. It is probable that the after-contraction is mainly an after-discharge from the cortex or its projection pathways, though modifiable by other parts of the nervous system. The after-contraction can be utilized in the investigation of the physiologic behavior of the cortex and in the study of drugs used in controlling its excitability. The phenomenon may possibly play a role in the formation of habits.

The Significance of Left Auricular Dilatation in Auricular Fibrillation. M. L. Sussman and M. T. Woodruff. Am. J. Roent. & Rad. Ther. 40: 184, August 1938.

(*1*) Analysis of the records of 96 cases of auricular fibrillation which had been studied by adequate roentgenologic or postmortem examination confirmed the current impression that the size of the left auricle was not directly related to the presence of the fibrillation. (*2*) Where the left auricle was enlarged in the non-rheumatic group there was uniformly an accompanying congestive failure. (*3*) Disproportionate left auricular enlargement in the non-rheumatic group was usually to be accounted for either by "mitralization" or by myocardial disease. (*4*) Auricular fibrillation of many years' duration may occur without auricular enlargement. (*5*) Dilatation of the left auricle in hyperthyroidism is usually associated with auricular fibrillation and congestive failure.

Diffuse Dilatation of the Pulmonary Artery. B. S. Denzer and H. Horn. Am. J. Dis. Child. 56: 608, September 1938.

A child was observed from the age of 3½ months with the characteristic signs of patent ductus arteriosus. At the age of 11½ years pulsating shadows were observed on fluoroscopy in the right hilar region, confirmed by X-ray examination. This condition is associated with many and varied congenital and acquired lesions of the vessels and has been reviewed by B. S. Oppenheimer. In children it is comparatively rarely referred to. The pathogenesis of the type described by us depends on increased pressure in the pulmonary vessels. Apparently the clinical condition has not been modified by the occurrence of pulmonary dilatation. Frequency and significance of these findings will depend on fluoroscopic observations in large groups of children suffering from congenital cardiac disease.

The Differential Diagnosis of Hyperparathyroidism. With special reference to Polyostotic Fibrous Dysplasia. J. H. Garlock. Ann. Surg. 108: 347, September 1938.

The author discusses at length the laboratory and roentgenologic aspects of hyperparathyroidism as aids in the diagnosis of this condition. Two cases of proved hyperparathyroidism are presented. In contradistinction to these, there is described in detail the history of a patient presenting all the evidence pointing towards the existence of hyperparathyroidism, including a negative calcium balance, but which, after bone biopsy, was proved to be polyostotic fibrous dysplasia. The author concludes that the surgeon, when confronted with suspicious bone lesions in the roentgenograms, and serum estimations of calcium and phosphorus outside the normal limits, and in spite of a negative metabolic balance of calcium, should not be too hasty in advising exploration of the neck for a parathyroid adenoma. It is suggested further that, when doubt exists as to the diagnosis, additional investigation should be undertaken to clarify the situation, consisting, first, of roentgenologic examination of the skeleton to determine whether the bone lesions have a predominantly unilateral distribution and, second, the performance of a bone biopsy. The latter will definitely establish the diagnosis by differentiating the characteristic histologic pictures of polyostotic fibrous dysplasia and hyperparathyroidism.

Thrombophlebitis of the Periprostatic Plexus. A. Hyman and H. Leiter. J. Urol. 40: 403, September 1938.

In this paper phlebitis of the periprostatic plexus is shown to be a distinct clinical and pathological condition. It is frequently unrecognized and camouflaged by the general term of "sepsis." The factors concerned in the etiology and pathology, as well as the clinical symptoms and findings, are presented in some detail. The differential diagnosis from other causes of sepsis are discussed. Eight fatal cases with post-mortem findings are presented at length. The paper concludes with the discussion of the problem of prophylaxis and treatment of this condition.

Bilateral Congenital Ectopia Lentis with Arachnodactyly (Marfan's Syndrome). J. Laval. Arch. Ophth. 20: 371, September 1938.

A review of this condition is given, separating those signs due to mesodermal changes from those due to ectodermal changes. A review of the literature from 1896 to the present is included and two new cases are reported, one a male fifty years old and the other a girl ten years old. Both patients showed the typical mesodermal changes characterized by long extremities, long, thin hands and feet, a lack of subcutaneous fat, long delicate fingers ("spider digits"—arachnodactyly), some scoliosis, long narrow teeth and a narrow bony palate with a high arch. Both further showed ectodermal changes characterized by miosis, dislocated lenses and rigidity of the pupils.

A new terminology is suggested so that the term dysmesdactyly would be used when the changes are primarily mesodermal without ocular involvement and the term dysmesectopia would be used when there are both mesodermal and ectodermal changes with resultant ocular involvement. It is further shown that the dilator muscle is not absent in these cases but may be somewhat rigid occasionally.

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CONTENTS

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DIGITALIS AND STROPHANTHIN

Their Relative Therapeutic Values and Practical Use[1]

ERNEST P. PICK, M.D.

The effective substances in the leaf of digitalis and related drugs are glucoside which are very complicated substances with a nucleus of 23 to 24 carbon atoms. This nucleus is like an ester bound to different sugars: digitoxose, cymarose, rhamnose, but also to glucoses and pentoses, and sometimes, even to two or three different sugars.

THE ROLE OF SUGAR COMPONENTS IN THE ACTION OF GLUCOSIDE

These sugar components give the specific character to the molecule-entity and furthermore, determine its solubility and still more important, its power to become fixed in the tissues and, above all, in the heart muscle (2). Glucoside which have lost their sugar components by any process whatsoever have at the same time lost part of their specific effectiveness. Since such decompositions can take place as the result merely of bad storage of the leaves, as, for example, in moist air, it is naturally important to know if the digitalis powder administered to the patient has retained its effectiveness. This might be ascertained by an assay of the drug on frogs or cats. Therefore, it is the duty of the physician who prescribes digitalis leaves or powder to request standardized products without exception.

In the *determination of the constitution* of the glucoside it is important to bear in mind that these sugars can be split off from the entire glucosid molecule either through the action of specific ferments or by means of acid-hydrolysis. Thus, one succeeds in gradually reducing these complicated substances and in changing a glucosid containing three molecules of sugar, a triose, into one with two sugars, biose, or into such containing one sugar only. One finds an interesting example of this fact in the determination of the structure of the complicated glucosid-mixture in the *Kombe-Strophanthin* (see fig. 1). This Strophantho-triose containing three sugar molecules can be reduced by gradually splitting off the sugar molecules with the aid of different specific ferments: first by the use of α-glucosidase-ferment into the crystallized K-Strophanthin; then by splitting off a second glucose molecule by another specific ferment-strophantho-biase—the *glycosid cymarin* could be formed; while the sugar molecule of *cymarin*,

[1] Lecture delivered March 4th, 1940 at the Rudolf Virchow Medical Society, New York Academy of Medicine, New York City.

the *cymarose*, cannot be split off by way of enzymes but only by acid-hydrolysis. The result is the *aglucone*, (so-called *genin*) constituting the nucleus of strophanthine, called *Strophanthidin*. One finds similar relations in the splitting of the *digitalis glucosids* carried out by Jacobs and Stoll (4). They made use of other specific ferments, such as the *digipurpidase* obtained from digitalis purpurea, and *digilanidase* derived from digitalis lanata (see fig. 2) or scillarenase, the enzyme contained in squill.

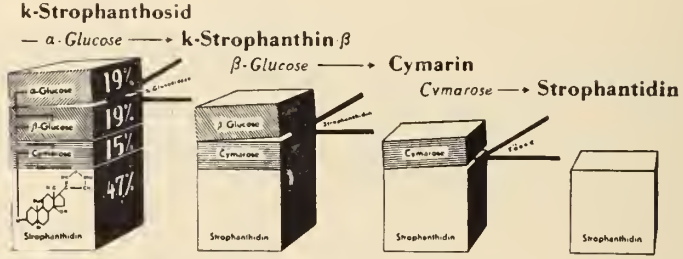


Fig. 1. Disintegration of Kombe-Strophanthin by α-glucosidase, strophanthobiase and acid-hydrolysis (graphs after Ch. Hentze, Sandof Chem. Works, New York, 1940).

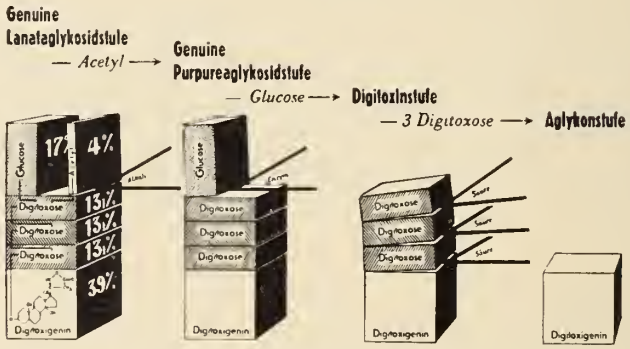


Fig. 2. Disintegration of Digitalis glucoside by alklienzym- and acid hydrolysis (graphs after Ch. Hentze, Sandof Chem. Works, New York, 1940).

THE CHEMISTRY OF GENINS

The nucleus of the glycosid, *aglucone* or *genin*, commands much greater interest than its sugar-components. The results of the determination of its constitution were such as to lead to the belief that the day is near when the synthesis of these glucoside and the artificial production of one of the most valuable remedies for the human heart will be possible.

The discovery of the aromatic carbohydrate *Methylcyclopentenophenanthren* as a split product of genin as well as sterine and bile-acids has revealed the close relationship of the genins with the cholesterin and, particularly, with cholan-acid. Thus, the heart glycoside show a far reaching constitutional relationship with a great series of important substances of animal-

and plant life as, for example, with the different cholesterin derivatives which we now know as *sex hormones, adrenal cortex hormone* (Corticosteron), *vitamin D, bile acids*, etc. (5) (fig. 3).

The known constitution of the pure glucoside and genins explains the fact why any change in the genin complex also may alter the effectiveness of the glucoside. The most sensitive part of the compound is the unsaturated five-valent *lactone ring* which is attached to C17. This lactone ring is easily saponified by alkalies causing the total loss of its heart-effect. Furthermore, certain enzymes contained in the strophanthus seed, independent of the process of splitting off sugars, may cause the change of effective glucosids into the ineffective genins. Since the effect on the heart of all free genins of the known glucosids, in contrast to that of the unsplit glucosids, is exceedingly small if not entirely absent, none of these genins is used in therapy. All therapeutically employed digitalis substances are, more or less, unsplit glucosids. Although all known genins are similar in their fundamental structure, they differ, however, from each other chemically and pharmacologically. This difference is still further enhanced by the kind and number of the attached sugar-groups. Thus, each glucosid has a specific and particular effect which can not be substituted at will through another glucosid.

THE BIOLOGICAL STANDARDIZATION OF DIGITALIS

The standardization of the digitalis glucosids through assay on frogs or cats has proved necessary because the chemical determination methods have failed. The knowledge, however, of the effect of these, partly very poisonous, substances is essential. The examination is designed to determine the amount of effective substances contained in the drug to be used, or in the pure glycosid, so as to facilitate the preparation of drugs, as uniformly effective as possible and so well standardized that they can be used without any danger to the patient.

The United States Pharmacopeia prescribes the biological evaluation on frogs (rana pipiens); in this method, the preparation to be examined is compared in its effect with "International Standard Digitalis Powder." "One international digitalis unit" represents the activity of 0.1 Gm. of the international standard digitalis powder which is equivalent approximately to 150 frog-units. *One frog-unit* is an amount of digitalis glycosid which kills one Gram frog within one hour; this is calculated to correspond to the amount necessary to kill a frog of 25 Gm. when the drug is injected into the ventral lymph sac. The *cat-unit* is found by determining the amount of drug required to stop the heart when slowly injected intravenously into a decerebrated cat. This quantity per kiloweight is a cat-unit.

Both methods are not without error, caused by variations due to season, temperature, species, weight, etc. In order to avoid all possible sources of errors, the evaluation is made by using generally acknowledged Inter-

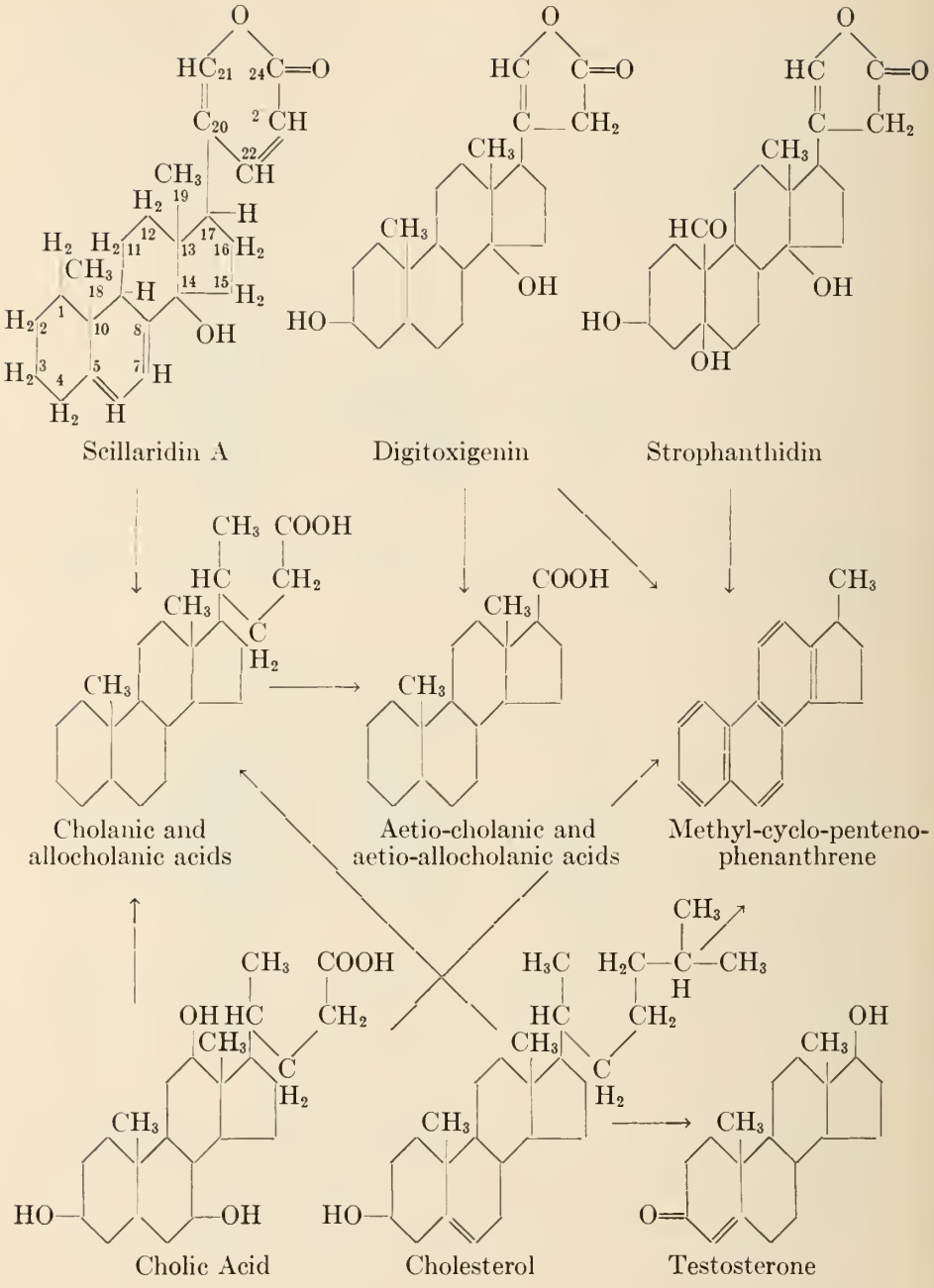
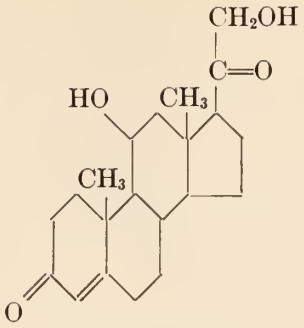


Fig. 3A

Fig. 3A and 3B. Constitutional relationship of heart glucosides with different cholesterine derivatives (graphs partly after A. Stoll, 1938).



Corticosterone

FIG. 3B

national Standard Preparations. It should be emphasized that the ratio between frog and cat doses is not constant in the different digitalis preparations, and has to be evaluated anew from time to time. A comparison of the relative amounts, therefore, is not possible, according to present experiences.

What relations, therefore, exist between the frog and cat-units as established by biological evaluation and their respective therapeutic values and uses? These units neither can nor ought to serve as bases of therapeutic dosage, nor may they be used for comparing the therapeutic value of different digitalis glucosids. They give us only those values which have been gained on the basis of lethal doses on frog- and cat-hearts. They say little if anything about the most important selective effects of those glucosides which alone are decisive in establishing their therapeutic influence on the impaired heart of *man*. Nobody will even think seriously of comparing the therapeutic potency of 150 frog-units of a tincture of digitalis with the potency of a tincture of strophanthin, or, for that matter, six cat-units of ouabain (Gratus-strophanthin) with as many units of Kombe-strophanthin or digitoxin (1). Toxicity and therapeutic potency do not always follow a parallel curve, though it is true that they may influence each other sometimes. Therefore, we must keep in mind that standard values, as elaborated in animal experiments, can not be used indiscriminately for therapeutic purposes. This is particularly true in the case of the diseased human heart which reacts differently to different digitalis glucoside. Hence, all attempts to test digitalis in the human had to be rejected as impractical, if not to say, impossible. Moreover, such a standardization has limited value for the treatment since many of these remedies contain a mixture of glucoside of different potency; which varies in accordance with place of origin and the season. Table 1 will serve as a revue of the minimal lethal frog- and cat-doses of several digitalis glycosides (3).

THE PHARMACOLOGY OF DIGITALIS GLUCOSIDE

A pharmacological analysis of the digitalis heart effect seems to be advisable and it is best to begin with the symptom-complex of the badly damaged heart, heart failure. The undamaged heart which beats normally can not be attacked at all by any therapeutic dose of digitalis. The decompensated heart in which the strength and rapidity of the systole and the duration of the diastole have been decreased tries to increase its initial filling and initial tension by dilatation. The increased filling of the dilated heart and consequently the increased strokevolume diminish the congestion. This mode of compensation can function only as long as the reserve power of the heart is sufficient. It leads to compensatory hypertrophy and dilatation. Many investigations, mainly by Starling and Visscher (6), prove that our heart-pump is one of the best equipped and

TABLE 1

Minimal lethal doses in mg. per 1 kg. weight

GLUCOSIDE PREPARATION	IN FROG DOSES	IN CAT DOSES
Digitalis powder	600	80
Digitoxin	2.5 6.0	0.318-0.420
Purpurea glycoside A	1.4	0.368
Digilanid (total)	1.6	0.343
Digilanid A	1.45	0.380
Digilanid C	1.56	0.280-0.400
Digoxin	1.6	0.280
Strophanthin U.S.P.	0.47-0.61	0.138
Ouabain	0.4-1.0	0.089-0.095
Scillaren	0.8-1.1	0.181
Cymarin	0.66	0.111
Convallatoxin	0.3	0.077

best functioning machines. It is capable of transforming about twenty per cent of about 400 calories consumed per minute into mechanical energy. Thus, it makes use of about one-fifth of the chemical energy while a steam engine can not transform into mechanical energy more than five per cent of the chemical energy. But Starling has found that heart dilatation demands heavy sacrifices in chemical energy. The more the heart dilates, the greater its oxygen consumption. The transformation of the liberated energy into mechanical effect, results in a very unfavorable ratio and may fall at times from twenty per cent to only three per cent, as (Harrison quoted by Visscher (7)) has found in chloroformed hearts. This ratio grows extremely unfavorable as the peripheral resistance is increased, as for example in hypertension. The same mechanical work, in increased peripheral resistance, is performed not only with higher oxygen consumption but also with perpetually increasing diastolic volume, which means in a very uneconomical way (8). Added to this is the pos-

sibility to which Katz and Mendlowitz (9) have called attention that in heart failure energy consumption may not be increased but there may be a lessening of energy liberation in the heart musculature.

Therefore, two demands are made on the heart glucoside which are supposed to increase the heart effect: *They must enable the weakened heart to perform a greater mechanical labor without exhausting its reserve power with dilatation and hypertrophy. The heart effect must be reached in the most economical way with an appropriate consumption of chemical energy approximate to the ideal conditions of the normal.* And, in fact, the digitalis glycosids fulfill these requirements in an excellent way, inasmuch as they improve the damaged heart functions and above all restitute the weakened heart muscle in its contractility and elasticity. All recent investigators studying the influence of the heart glucosids upon the energetics of heart action agree that the insufficient heart with its high oxygen consumption, its low degree of mechanical effectiveness and its progressively increasing diastolic volume is transformed by the digitalis glucoside into a heart which is able to perform a decided increase of mechanical labor, at lower oxygen consumption and decreasing diastolic volume (10). Thus, Gollwitzer-Meier and Kruger were able to prove on spontaneously insufficient dog hearts after administration of 0.25 mg. K-Strophanthin that a decrease of 12.5 per cent in oxygen consumption followed a decrease of the diastolic volume (7 cc.) and an increase of the mechanical work by 35 per cent. Visscher saw under similar conditions that the efficiency of the Starling heart rose from 1 per cent to 10 per cent after the administration of the digitalis glucosid. *The digitalis glucosids, therefore, increase the mechanical effect of the diseased heart without any greater energy expenditure.*

The finer mechanism of this unique effect on the muscle is as yet unclear. We have learned, however, that besides the effect on the muscle there is a great series of other digitalis effects which may be associated with the decrease in energy expenditure in the muscle. The most important of these are: The *vagal heart slowing* and the *retardation of conduction*, both serving the purpose of regulating the heart work as well as possible and of bringing it nearer the normal. How successfully this may be achieved is proved by experiments concerning the reaction of a weakened Starling-heart before and after strophanthin, at the same time exposing it to a greater influx of fluid (fig. 4). The action of strophanthin on the vagal heart slowing is exemplified in fig. 5. These *immediate* effects of the digitalis bodies which we can observe in pharmacological experiments are followed by *indirect consequences for heart and circulation;* the most important of which are: 1) *improved bloodflow through the heart;* 2) *the regularizing of the rhythm and frequency;* 3) *the decrease of the venous pressure* in the right auricle and in the veins near the heart; 4) the *relief of congestions* in the different organs; 5) initiation of *diuresis* and; 6) lastly, *regularizing of the blood pressure* and of the *circulating blood volume.*

A discussion of *therapeutic effect* of digitalis glycoside raises the question whether all the heart glycosid which, thanks to the unceasing efforts of the chemists, we have learned to recognize in their pure state, are able to render the same therapeutic aid and whether or not they are interchangeable. No matter how alike they are in the fundamental formulae of their chemical structure, they act therapeutically and clinically as very different bodies. We are accustomed to differentiate the glycoside, according to

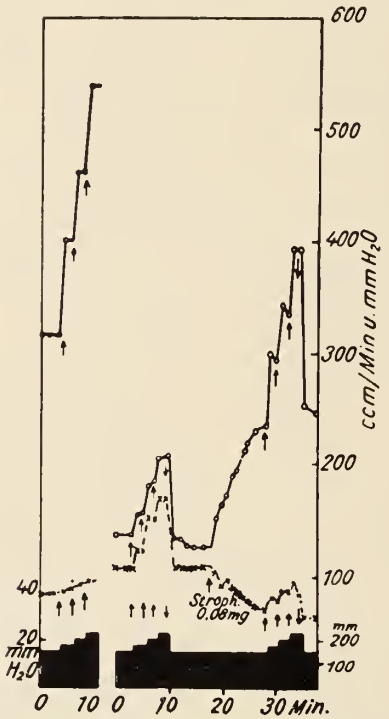


Fig. 4. Action of Strophanthin on the weakened heart in the Starling-heart-lung preparation (after Aritschkow and Trendelenburg: D. Med. Wchnschr, 1672, 1928). Solid black, blood supply; continuous line, minute volume; dotted line, auricular pressure. Increased blood supply leads to a rapid rise of minute volume in the normal heart. In the damaged heart, there is but a small effect of the increased blood supply on the minute volume; after administration of strophanthin (0.08 mg.) the response is nearly that of the normal. The rise of the auricular pressure in the damaged heart with an increased blood supply is greater than in the normal. Strophanthin removes this pathological response.

Straub (2) into two groups. The glycoside of the first order, contain the true digitalis glycoside-digitalis purpurea and digitalis lanata; whereas glycoside of the second order comprise the glycoside of the strophanthus seed, of scilla maritima, adonis vernalis, convallaria majalis, nerium oleander and others. The digitalis glycoside of the first order are distinguished by their power of fixation in the heart muscle (and also in liver, kidney and skeletal musculature), by their gradual effect which sets in only

slowly and by their cumulative action. Added to these qualities are the powerful vagal heart slowing and the very definitely pronounced inhibition of the conduction system. The second group with its main representative strophanthin, lacks the stronger fixation power and, therefore, cumulates less. It effects the diseased heart at once, it quickly raises its systolic effect and thereby indirectly quickens the passage of the blood through the heart without exerting a strong diminishing influence on frequency and heart-conduction. Newer researches have shown however, that the differences between the two groups, consisting mainly in the fixation and cumulation power of the digitalis bodies, are not fundamental.

FIG. 5. The effect of an intravenous injection of strophanthin upon the heart rate in a case of auricular fibrillation. The arrow denotes an intravenous injection of strophanthin, 0.25 mg. ($\frac{1}{250}$ gr.). (After Cushny et al., 1913.) (From A. J. Clark: Applied Pharmacology, London, 376, 1937.)

The reason for this is that the cumulative symptoms, shown to exist in animal experiments on cats, may probably be attributed to *heart muscle necroses* (11). These have been produced in experimental animals not only by administration of large digitalis doses, but also by strophanthin in comparatively greater amounts. Secondly, latest researches have discovered some digitalis bodies which have a strophanthin effect, working rapidly and with slight cumulation, as for example digilanid C (Cedilanid) (12). Nevertheless, there remain important differences. *Digitalis purpurea* with its most valuable glucoside digitoxin takes *effect slowly* and is fixed in the *heart muscle for a long time*. On the other hand the *sudden*

effect of the strophanthin glucosids without any strong fixation-power in the heart muscle presents differences which are enhanced by their mode of application. We know from old experiments by Hatcher, Eggleston, Hanzlik and Wood and by newer experiments carried through quantitatively by Weese and Rothlin (13) that only the smallest part (about 10 per cent) of the glycoside administered reach the heart. By far the largest part disappears into other tissues, mainly the liver, kidney and skeletal muscles. To this we must add that peroral administration with almost uncontrollable conditions of relative resorption almost excludes the use of sharply delimited doses. And yet, peroral application in the presence of good stomach function, is the most comfortable form of administration and the ideal mode of procedure for chronic digitalization. Only in cases in which congestive inflammation of the gastro-intestinal tract or congestion of other abdominal organs make oral application unsuitable, rectal digitalis application is to be preferred, since from the rectum, evading the liver circulation, this remedy may be conveyed directly into the sphere of the vena cava inferior and may reach the heart unimpeded by the liver. This mode of application is well known to all of you as a safe method of gradual digitalization.

If, however, heart failure threatens life acutely, *immediate relief* is frequently required. In such a case only the intravenous application of a *rapidly effective glycoside* can help the heart and save life. In such cases we can not turn for help to the slowly effective glycoside of the first order of the purpurea, not even to the otherwise excellent Digitaline Nativelle which is the first crystallized glycosid, the digitoxin of the digitalis purpurea, discovered by Nativelle in 1868 (0.1 mg. intravenously), nor to the somewhat weaker Digoxin (0.5–0.75 mg.) split off the lanata series, not even if they are given intravenously. In most cases their effect reaches a peak only after several hours.

According to present knowledge this is the indication for the use of the promptly effective *strophanthin glycoside* (14). The fundamental difference in effect between the digitalis purpurea, resp. digitoxin and the strophanthins, mainly the Kombe Strophanthin (crystallized K Strophanthosid) will be shown in table 2.

The United States Pharmacopeia contains only the Kombe-Strophanthin and it is with this amorph-preparation that the greatest number of experiences has been collected since the introduction of the intravenous strophanthin-therapy by Albert Fraenkel 35 years ago. The somewhat more toxic crystallized Gratus-Strophanthin has been employed in France for a number of years under the original African name of Ouabain (Arnaud).

Experience had shown that doses of *0.15–0.25 mg.* are sufficient in all cases and are free from unpleasant consequences. The bad accidents, strophanthin-death, due to ventricular fibrillation which have been observed in the beginning of the strophanthin-therapy and which have served

to discredit this excellent medication have been caused by overdosage. But as we know to-day there is no better remedy to combat *acute* heart failure than by *intravenous strophanthin.* No other form of administration permits so accurate a dosage of the pure substance. The systolic strength of the failing heart is raised immediately.

Fraenkel deserves the credit of having stimulated intravenous strophanthin-therapy by a lifetime of effort. This therapy requires a perfect intravenous injection technique as paravenous injection introduces the danger of serious local irritation.

The most important and probably the *only contra-indication* to intravenous strophanthin-therapy is a preceding digitalization. Even though digitalization may seem to have been without effect, it may be sufficient to make the heart hypersensitive to subsequent strophanthin-administration. This danger can be avoided by a rest period of two to three days, or, in cases of danger to life, by very slowly administering very small—if needs be repeated—doses of strophanthin of not more than *0.15 mg.* at most.

TABLE 2

	DIGITALIS PURP. DIGITOXIN	STROPHANTHIN KOMBE (K-STROPHANTHOSID STOLL)
1. Water solubility	Insoluble	Soluble
2. Fixation	Fixed	Not fixed (?)
3. Cumulation	Cumulates strongly	Cumulate slightly
4. Onset of effect	Slow	Immediate
5. Pulse	Much slowed	Slightly slowed
6. Conduction	Clearly inhibited	Slightly inhibited
7a. Peroral administration	Strongly effective	Not effective
7b. Rectal administration	Effective	Doubtful

But it is necessary to observe the patient during the first half hour after the injection for the appearance of extrasystoles. Onset of accumulated extrasystoles or bigeminy as symptoms of beginning *strophanthin poisoning* can be relieved by quinidine sulfate (0.2-0.3 Gm.) which will slow down the hyperexcited centres of heterotopic stimulus formation. In order to avoid the constrictor effect of strophanthin on the coronary vessels, which by the way is very much doubted by newer researchers, aminophylline (theophylline-ethylene-diamine) 0.5 to 0.6 Gm. has been recommended in form of suppositories, or a combination of the mercurials with theophylline (15) may be used. Also strophanthin 0.25 mg. together with Salyrgan or even better with Mercupurin often has an excellent effect in producing abundant diuresis and in reducing the liver swelling, an effect that can hardly be reached by digitalis preparations alone.

The glycoside of the *digitalis lanata* closely approach those of the strophanthins because of their quicker effect and their weaker cumulative ability. *Digilanid C* (*Cedilanid*) one of the three native glycosides of this

order has been recognized of late as the one with the strongest and quickest effect. Compared to strophanthins it has the advantage of good oral efficacy and great therapeutic breadth with a remarkable diuretic effect. It is well tolerated, locally less irritating than the strophanthin and its effect is strophanthin-like in as far as it hardly cumulates at all. The intravenous dose is *0.4 mg.* per day, the oral dose 1.5 to 2.0 mg. per day.

And now, which are the *vital indications* that justify the immediate intravenous administration of strophanthin? According to observations of competent cardiologists the following indications ought to be observed (16):

Acute heart insufficiency due to previously untreated hypertensive heart diseases, mitral stenosis during delivery, coronary diseases developing acute pulmonary edema and nephritis. In these and similar conditions with acute danger to life, it is not possible to wait until digitalis even given intravenously begins to act. Furthermore, in paroxysmal tachycardia with rapid onset of decompensation, an intravenous strophanthin injection may be of immediate value. Further treatment of the heart may then be continued by the more comfortable peroral route of digitalization. The reversed order digitalization followed by strophanthin intravenously is contraindicated.

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GASTRO-JEJUNO-COLIC FISTULA

Preliminary Colostomy with Spontaneous Healing of Transverse Colonic Fistula. Secondary Subtotal Gastrectomy with Partial Jejunectomy

RALPH COLP, M.D.

[*From the First Surgical Service*]

Jejunal ulcer following gastro-enterostomy, because of the tendency to spread, may either occasionally perforate into the free peritoneal cavity, or at times involve the transverse mesocolon and penetrate into the colon. The fistula generally connects the efferent jejunal loop and the transverse colon and lies quite close to the gastro-enterostomy stoma. Immediate surgical treatment is the only method by which a rapid death from inanition may be prevented.

CASE REPORT

History. (Adm. 426675). N. W., a 49 year old male was first admitted to the hospital on January 7, 1935. He gave a nine year history of intermittent attacks of epigastric, post prandial burning pain associated with nausea, occasional vomiting, eructations, and pyrosis. For several months before admission, the pain had been almost constant and was worse after meals. He had also noted at this time post prandial epigastric distention and frequent vomiting after meals. The vomitus occasionally contained food eaten several days before, but never any blood. There was no history of melena. One week before admission, a gastro-intestinal X-ray series was done and a penetrating duodenal ulcer with a large gastric residue after five hours was found.

Examination. The patient was well-nourished and well-developed. The only positive finding was slight tenderness in the epigastrium, more to the right.

Laboratory Data. Gastric aspiration revealed a retention of ten ounces containing food eaten many hours before. The stool was guiac positive. Hemoglobin was 65 per cent. Urine examination was negative. A Rehfuss test meal revealed a maximum total acid of 90, maximum free acid of 64. Urea nitrogen, 20 mg., sugar, 105 mg., chlorides, 555 mg., CO_2 60.5 volumes per cent. The blood Wassermann reaction was negative. An electrocardiogram showed left ventricular preponderance and low voltage, the latter possibly indicating a poor functional condition of the heart.

Operation. It was decided that surgical exploration was justified because of the long duration of the patient's symptoms, and especially in view of the advancing pyloric stenosis. Accordingly, on January 12, 1935, under spinal anesthesia, through a median epigastric incision, a retrocolic posterior no loop gastro-enterostomy was performed for chronic duodenal ulcer producing a partial pyloric obstruction.

Course. The post-operative course was uneventful and he was discharged twelve days after operation. The patient felt fairly well until three months before his second admission when he again began to have frequent bowel movements accompanied by the belching of fecal tasting gas. He had lost ten pounds during this period. Barium enema revealed the presence of a gastro-jejuno-colic fistula.

Second Admission. He was re-admitted to the hospital on April 13, 1938. He appeared to be well-nourished. He belched frequently with a feculent odor apparent on the breath. There was a small incisional hernia at the previous operative site. The hemoglobin was 70 per cent. The urine was clear. The blood chemistry was normal. An electrocardiogram was negative. A night Rehfuss test meal revealed a free acid of 80 and a total acid of 128. When a methylene blue enema was administered to the patient, the dye appeared twenty minutes later through a gastric Levin tube establishing the presence of a gastro-jejuno-colic fistula.

Operation. On May 6, 1938, under spinal anesthesia, and through an upper right rectus muscle splitting incision, the ascending colon was mobilized. Crushing clamps were applied to the midportion of the colon which was exteriorized while the

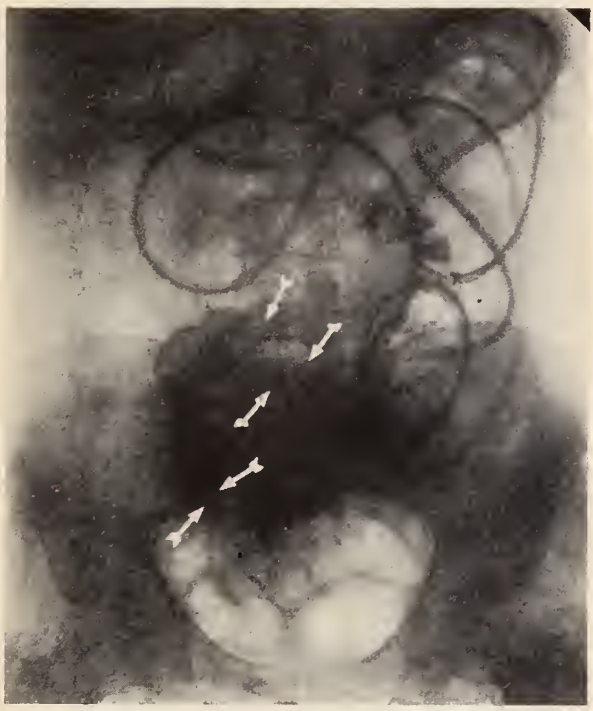

FIG. 1. Roentgenogram taken with barium introduced through Miller Abbott tube. Arrows point to stenotic areas in ileum.

distal and proximal limbs were united to form a spur. The colon was divided between the clamps.

Course. The proximal colonic loop was opened twenty-four hours after operation and the clamps were removed on the sixth day. Almost immediately the patient noted that his breath was no longer fecal. At the time of discharge, the entire fecal stream was side tracked and draining well through the lower colostomy opening. The distal colonic segment, however, was still in communication with the stomach as was evidenced by the appearance of methylene blue in the gastric Levin tube twenty minutes after the dye had been administered in an enema. He was discharged on May 17, 1938.

Third Admission. The patient reentered the hospital on July 8, 1938. He was asymptomatic and had gained about eighteen pounds. A gastro-intestinal series

showed evidence of a previous gastro-enterostomy. The barium mixture passed through the stoma which was tender and irregular; within the jejunum about two inches from the stoma, a large ulcer pocket, one inch in diameter, was observed. There was no evidence of a gastro-jejuno-colic fistula. A barium enema injected through the colostomy showed irregularity of the midportion of the transverse colon but no communication between the colon and stomach (fig. 1).

Fig. 2 (Upper). X-ray studies of small bowel showing enormous dilatation proximal to site of fecal fistula. At this point the bowel was almost completely divided by the marked stenosis.

Fig. 3 (Lower). Photograph of resected distal loop of small bowel revealing the sites of fistulous openings and aboral stenotic area.

Operation. On July 16, 1938, under anesthesia, the scar of the previous median epigastric incision was removed. In the region of the previous gastro-enterostomy there was a hard inflammatory mass about the size of a lemon which included the stomach, colon and jejunum. About twelve inches from the duodenal jejunal angle, the efferent jejunum was found to be the seat of a definite ulceration almost opposite the neostomy. The fistula in the colon had evidently healed and was replaced by hard fibrous indurated connective tissue (fig. 2). The stomach itself was dilated to about twice its normal size and this was apparently due to a stenosis at the duodenum

due to a healed duodenal ulcer. A partial jejunectomy with end to end jejuno-jejunostomy for a jejunal ulcer and a subtotal gastrectomy with a Hofmeister ante colic gastro-enterostomy for healed ulcer of the duodenum with pylorie stenosis was performed. The pathologist reported the following:

"Specimen consists of a resected stomach and a short loop of small bowel (fig. 3). In addition, there is a small fragment of bowel measuring 4 cm. Apparently a gastro-enterostomy had been performed some time previous and the present operation consists of a partial jejunectomy and a subtotal gastrectomy. The lesser curvature measures 12 cm. The greater curvature measures 22 cm. The stomach and small bowel were received separately. The opening of the jejunum into the stomach is located 7 cm. from the duodenal line of resection. The mucosa of the stomach is hypertrophied and injected. The rugae are very prominent throughout. This is particularly true in the region of the gastro-enterostomy opening. The gastric mucosa has been stripped from the submucosa around the circumference of the gastro-enterostomy opening. This is probably an artefact. There are no obvious ulcers on the gastric side of the gastro-enterostomy. The attached ligaments are thin and one small gland was removed from the omentum. The small fragment of jejunum described above shows hemorrhage, hypertrophy of the mucosa, but no ulcer. The other loop of small bowel shows marked searring and thickening of the serosa in one area. However the mucosa opposite this mucosal scarring does not show any ulcer. The mucosa throughout is hypertrophic and injected. Diagnosis: Chronic peptic ulcer of the jejunum."

Course. After a moderate fever reaction and some gastric regurgitation, the patient did well. A spur crusher was applied to the colostomy two weeks after operation, and two weeks later, an extraperitoneal closure of the colostomy was performed under ethylene by Dr. P. Klingenstein. Patient was seen on March 1, 1939, at which time he looked and felt well. He had gained twenty-five pounds since his operation.

COMMENT

There are many operations which have been designed for the surgical treatment of gastro-jejuno-colic fistula depending upon the pathologic conditions present at the time of operation. A discussion of these various procedures does not concern us here. Most surgeons are now convinced that degastro-enterostomization with or without colonic resection is an inadequate procedure. The aim of any operation employed, therefore, should be the elimination of the jejunal ulcer by excision, the restoration of colonic continuity, and the performance, either simultaneously or eventually, of an adequate gastrectomy. Whether this is done in one or multiple stages depends upon the condition of the patient, the judgment and skill of the operator.

At a combined meeting of the Philadelphia Academy of Surgery and the New York Surgical Society held in February, 1938, Dr. Damon Pfeiffer presented a patient with a gastro-jejuno-colic fistula on whom he performed a preliminary ascending colostomy with the formation of a spur, insuring a complete diversion of the fecal current. He felt that much of the inflammatory exudate present about these lesions would be diminished by this procedure, making any necessary subsequent surgery much simpler. His premise was substantiated not only in the case which he presented at

that time, but in the patient presented here. In this man, a gastro-jejuno-colic fistula developed about three years after a posterior gastro-enterostomy for a penetrating duodenal ulcer with pyloric stenosis. Inasmuch as the patient was not in good physical condition, it was decided to perform an ascending colostomy first. Within twenty-four hours after the colostomy, he lost the feculent belching although at the time of his discharge the colonic fistula was still present.

Upon a readmission to the hospital three months later, his physical condition had greatly improved and he had gained eighteen pounds in weight. The colonic fistula had healed spontaneously, as was proved by barium studies of the stomach and colon. At the time of the second operation the inflammatory reaction present was not insurmountable and the partial jejunectomy and subtotal gastrectomy were performed with little difficulty. About three weeks after this procedure, the colonic spur was crushed and an extraperitoneal closure of the ascending colon was done.

This procedure is rather prolonged. It appears, however, to be a logical operation, in that the colostomy, by the complete diversion of the feces, evidently caused a recession in the reaction present and in this particular case led to a spontaneous closure of the colonic fistula. Then, too, the general physical condition of the patient was materially improved following this procedure so that he became a better candidate for the future radical surgery.

CONGENITAL BILATERAL HYDRONEPHROSIS SIMULATING POLYCYSTIC KIDNEYS

BERNARD S. WOLF, M.D.

(*From the Surgical Service of Dr. A. Hyman*)

The polycystic kidney as a disease entity is well known and frequently diagnosed. The condition of bilateral hydronephrosis is much rarer. Because of this, it is rarely thought of when a uremic patient with enlarged kidneys presents himself. As a result, surgical therapy which can be curative is postponed to a time when the operative results are much poorer, or even nil. The following case is an example of this condition.

CASE REPORT

History: (Adm. 441982) S. H., a 17 year old girl was admitted to the service of Dr. George Baehr on June 14, 1939. Admission diagnosis was "polycystic kidneys."

There were no siblings. The family history, while incomplete because of the disappearance of the mother, was non-contributory. The patient had never been a particularly healthy child, suffering from frequent colds and sore throats. At the age of 7 months, she had an episode of bronchopneumonia, complicated by bilateral otitis media. From the age of two years, and particularly to the age of five and a half years she experienced frequent episodes of anorexia, nausea and vomiting, which persisted for several days. Tonsillectomy and adenoidectomy were performed at the age of five and a half years, after which these episodes diminished in frequency. At the age of seven, she complained of frequent frontal headaches, which were only partly relieved by the fitting of glasses. The menses started at the age of 12 years, lasted four days with an interval of 28 days and were regular until 14 months before admission, when they suddenly stopped completely. The last menstrual period was on July 21, 1938.

Four and two years before admission she experienced episodes of mild epistaxis. Her average weight during the past two years was between 90 and 98 pounds. At the age of 16½, despite considerable sickness, she was in her sixth term of high school.

Six years before admission, at the age of 11, she was seen by a physician because of anorexia and she was said to be anemic. She was given iron and liver therapy, but without marked improvement in her general condition.

Four years before admission, while walking upstairs, she was suddenly seized with pain in both lumbar regions, radiating anteriorly towards the umbilicus. The pain caused her to double up, and any movement increased the pain. She was rushed by ambulance to a hospital, where she remained for two weeks. During this period she vomited frequently, and she recalls that bilateral costovertebral angle tenderness was present.

Four days after discharge she was again suddenly seized with severe pain, similar to the first episode, and she was hospitalized at a second hospital for a month. Three cystoscopic examinations were performed, and on discharge, the family was told that the patient had enlarged kidneys.

She then was relatively well until about two years before admission, when the

episodes of nausea and vomiting became more frequent. In addition, she began to have spasms of her fingers and toes and of the calf muscles. The fingers became flexed at the metacarpo-phalangeal joints and extended at the phalangeal joints. The toes became plantarflexed. These spasms lasted for 2 to 3 minutes, were painless, and disappeared spontaneously. They also occurred, but were not more frequent, at night and awakened her from sleep. They occurred anywhere from several times a day to two or three times a week. A physician prescribed calcium, strychnine and liver extract and on this regime the spasms diminished in frequency.

A year and a half before admission, she had an episode of cough and mucoid expectoration lasting two months. This condition was diagnosed as bronchopneumonia.

Three months before admission she was readmitted to the second hospital because of abdominal pain, nausea, and vomiting. She also had mild diarrhea lasting four days, and a purplish, ring-like rash on her legs which was not hemorrhagic. Two cystoscopic examinations were performed. The blood urea nitrogen was 90 mg. per cent and CO_2, 31 vol. per cent. She remained in this hospital for six weeks. On discharge, the family was told that the patient had polycystic kidneys and that the prognosis was hopeless.

After discharge, she continued to complain of almost constant anorexia, headache and irritability. The spasms had, however, practically disappeared. During the month before admission she developed polydypsia, drinking as much as five quarts of water a day. The week before admission she noted polyuria, daytime frequency of nine times, and nocturia one time.

Examination: Examination on admission showed a well-developed, fairly well-nourished, comfortable, cooperative girl. The temperature was 99°F.; pulse 92 per minute, respiration 20 per minute. The fundi were normal. There were a few small posterior cervical nodes. The heart was not enlarged. P2 was markedly accentuated. The blood pressure was 112 systolic and 70 diastolic. There were bilateral Chvostek signs. The skin of the face and back showed numerous papules, comedones and occasional pustules. She had a peculiar brownish pallor. An enlarged right kidney was easily palpable. The left kidney was not definitely palpable.

Laboratory data: The hemoglobin was 65 per cent. Red blood cell count 4.7 million. White blood cell count 6,400 with 62 per cent segmented polymorphonuclear leucocytes, 5 per cent non-segmented polymorphonuclear leucocytes, 30 per cent lymphocytes and 3 per cent monocytes. Sedimentation time was 1 hour and 20 minutes by the Lindenmeier method. The stool was brown and guaiac negative. The urine on admission was alkaline, contained a trace of albumin and an occasional white blood cell. A urine concentration test was performed and showed the following results: 7 p.m. to 7 a.m., 1025 cc., 1.008 sp. gr.; 8 a.m., 60 cc., 1.010 sp. gr.; 9 a.m., 125 cc., 1.008 sp. gr.; 10 a.m., 50 cc., 1.008 sp. gr.; 11 a.m., 50 cc., 1.008 sp. gr.

The blood urea nitrogen was 56 mg. per cent, creatinine 5.6 mg. per cent, cholesterol 370 mg. per cent, phosphorus 5.2 mg. per cent, calcium 10.4 mg. per cent, albumin 5.2 grams per cent, globulin 1.4 grams per cent, and CO_2 content 45.2 vol. per cent. Repeated blood chemistries later in her course showed that the phosphorus was 4.9 mg. per cent, calcium 9.4 mg. per cent, phosphatase 16 and 14 King-Armstrong units, total cholesterol 260 mg. per cent and cholesterol ester 120 mg. per cent. The blood Wassermann reaction was negative. An electrocardiogram showed no abnormality. X-ray examinations of the skull and long bones were negative. A flat-plate of the abdomen showed enlarged kidneys on both sides. Intravenous pyelogram was performed and showed no visualization on either side.

Course: The diagnosis of polycystic kidneys seemed to be relatively certain. Despite this, however, the Urological Service was requested to see this patient. They felt that cystoscopy and retrograde pyelogram on one side were indicated in

order to conclusively prove the diagnosis. Cystoscopy was, therefore, performed and both ureters were catheterized. No indigo carmine appeared from either side in 45 minutes. A left retrograde pyelogram was attempted. When the plate was developed (fig. 1), it was seen that none of the solution had entered the kidney pelvis. The catheter had not passed the ureteropelvic junction. Because of this, cystoscopy was repeated and the attempt was made to do a retrograde pyelogram on the left side with a No. 9 Garceau catheter. After 6 cc. of hippuran was injected, the patient complained of severe pain. A plate taken at this time again showed no solution in the pelvis. A No. 9 Garceau catheter was then passed up the right ureter and 15 cc. of hippuran was injected. This plate showed an obvious marked hydronephrosis (fig. 2). In addition, after 10 minutes in the erect posture, the pelvis did not empty.

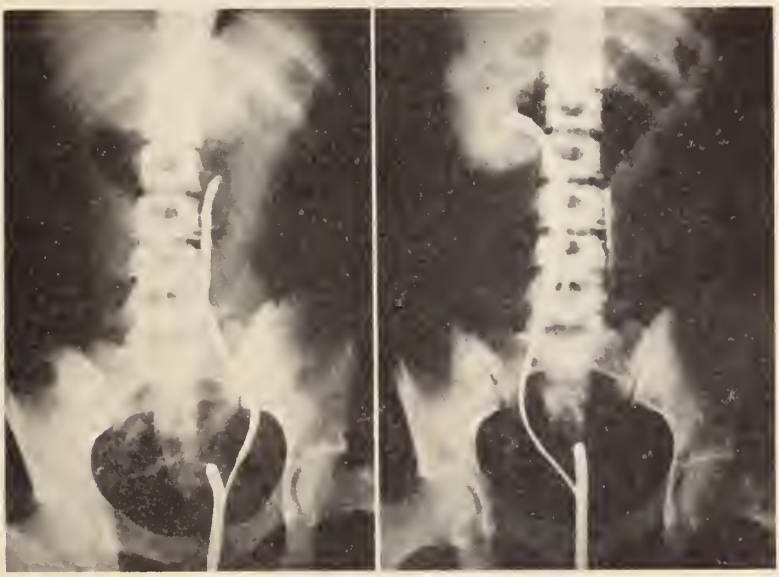

FIG. 1 FIG. 2

FIG. 1. Attempt at left pyelogram, demonstrating complete block at the ureteropelvic junction.

FIG. 2. Right uretero-pyelogram, demonstrating marked hydronephrosis; catheter blocked at the uretero-pelvic junction.

The diagnosis then was changed from polycystic kidneys, which is a hopelessly incurable disease to bilateral hydronephrosis on the basis of bilateral uretero-pelvic strictures, which is a surgical problem.

The first step in the surgical attack was an exploration of the left kidney, the side which was completely occluded. Under avertin and ethylene anesthesia, a large hydronephrotic kidney with considerably thinned-out parenchyma was exposed. The upper two inches of the ureter seemed to be almost completely occluded. It was impossible to pass even a No. 5 ureteral catheter from above or below. The ureter below the stenotic portion appeared to be normal. A typical nephrostomy through the convex border of the kidney was performed.

Post-operative course was complicated by the appearance, three days post-operatively, of a bronchopneumonia involving both lower lobes. The general condition of the patient was quite poor. Therefore, despite the poor renal function,

sulfapyridine was considered to be indicated. Over a period of 9 days, 28 grams were administered, 4 grams being given by rectum because of nausea and vomiting. The maximum blood sulfapyridine concentration was 10.1 mg. per cent. Twelve days post-operatively, the temperature returned to normal and the chest was clear. As soon as the sulfapyridine was stopped, the temperature again gradually rose and for the next two weeks ranged between 101° and 102°F.

During the first two weeks post-operatively, the drainage from the left nephrostomy averaged 20 to 25 ounces. It was clear, with a specific gravity of 1.004, and showed an occasional white blood cell on microscopic examination. She voided an average of 30 ounces. Six days post-operatively, the blood urea nitrogen fell to 24 mg. per cent.

During the next two weeks, the nephrostomy drainage diminished in amount to 8 to 10 ounces a day, it became cloudy, the specific gravity of 1.010, and showed numerous single and clumped white blood cells. Culture of the drainage showed B. pyocyaneus, B. coli and enterococcus. Culture of the urine from the right kidney obtained by ureteral catheter, showed B. pyocyaneus. No indigo carmine appeared from either side. The blood urea nitrogen gradually rose to 62 mg. per cent.

At this time, approximately four weeks after the first operation and six weeks after admission, the right kidney was explored under avertin and ethylene anesthesia. A large hydronephrotic kidney with moderately dilated pelvis was found. The upper portion of the ureter was buried in adhesions, angulated and tortuous, with an abnormally high exit from the pelvis. The upper portion of the ureter was freed from adhesions, following which there appeared to be free drainage from the pelvis to the ureter. A small pyelotomy opening was made and the attempt was made to pass a ureteral catheter down the pelvis. This was unsuccessful. A small opening into the ureter was then made below the uretero-pelvic junction, and a ureteral catheter was passed upward and out through the pyelotomy opening and then down the ureter into the bladder. A nephrostomy was then performed using the Kimball nephrostomy hook.

The ureteral catheter was allowed to remain in place for 11 days. The right nephrostomy functioned satisfactorily, draining from 30 to 105 ounces of urine daily. Drainage from this side was practically clear. The specific gravity of the urine was 1.010; it was slightly alkaline, and showed an occasional white blood cell on microscopic examination. Culture showed B. pyocyaneus, B. coli and enterococcus. The blood urea nitrogen fell progressively to 10 mg. per cent six weeks after right nephrostomy was performed. The drainage from the left nephrostomy, however, diminished to $\frac{1}{2}$ to 1 ounce a day, became grossly purulent, and on culture showed B. pyocyaneus, B. proteus, B. coli and enterococcus. She ran a continuously septic course, with temperature ranging between 101° and 103°F. for a period of seven weeks. Two blood cultures were negative. Despite adequate amounts of iron and four transfusions, the hemoglobin could not be raised above 40 per cent. Her general condition was definitely slowly deteriorating. Eight grams of sulfanilamide were given, but the patient became markedly confused and the drug had to be stopped. It became obvious that a pyonephrotic kidney was present on the left side which would have to be removed.

Seven weeks after the second operation and thirteen weeks after admission, a left subcapsular nephrectomy was performed under cyclopropane anesthesia. The nephrostomy sinus tract was completely occluded. The resected kidney had diminished markedly in size. The pelvis and the dilated calyces were filled with thick pus. Examination of the resected kidney showed complete absence of any communication between the pelvis and ureter, i.e. the uretero-pelvic junction was completely closed (figs. 3 and 4). The upper two inches of the ureter appeared narrow. Microscopic examination of the kidney showed acute and chronic pyelo-

nephritis and no evidence of any primary disease such as tuberculosis, which might have been the cause of the uretero-pelvic stenosis. Microscopic examination of a

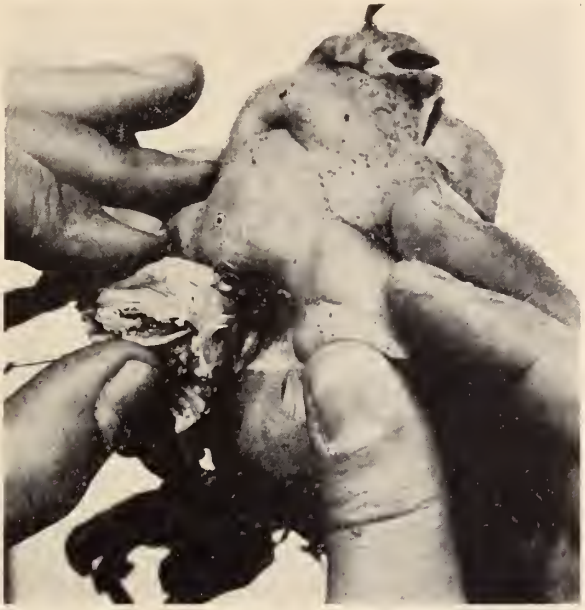

FIG. 3. Resected left kidney. Probe through narrowed ureter; just proximal to this, lumen was entirely obliterated.

FIG. 4. Resected left kidney, opened along greater curvature; pus has been evacuated. No evidence of any uretero-pelvic communication.

section through the hilum of the kidney just distal to the point of complete stenosis showed marked narrowing of the ureter by fibrous tissue.

A week after the third operation, the temperature subsided to 100°F. The general condition of the patient improved rapidly. The blood urea nitrogen was 22 mg. per cent. With one blood transfusion and iron by mouth, the hemoglobin became elevated to 82 per cent. Indigo carmine appeared in the right nephrostomy drainage in good concentration in 10 minutes. She began to void larger amounts, 10 to 36 ounces a day.

Because of this marked improvement, it was decided to investigate the possibility of removing the nephrostomy tube. A solution of 40 per cent hippuran was injected into the tube and outlined the pelvis, ureter and bladder. The nephrostomy tube entered the lower calyx; the ureter appeared to be straight. The hydronephrosis, though still considerable, had decreased markedly. The solution was injected under moderate pressure before much of it passed into the ureter. Despite this, however, the nephrostomy tube was clamped off for a period of three days. During this time there was considerable leakage about the tube and she voided only about 10 ounces each day. The blood urea nitrogen rose to 42 mg. per cent and the temperature rose to 101°F. Because of this it was decided that the nephrostomy tube would have to remain in place, at least for the present. She ran a low-grade fever between 100° and 101°F. for a week, after which it subsided to normal. The blood urea nitrogen, however, remained at 43 mg. per cent for almost a month and then fell to 27 mg. per cent.

Forty-one days after the last operation, the patient had an exacerbation of pyelonephritis with temperature between 102° and 103°F. for a period of 4 or 5 days. This subsided on forcing fluids without any urinary antiseptic. Urine culture showed B. coli, enterococcus, B. pyocyaneus and B. proteus.

On discharge, the temperature had been normal for three weeks. The urine showed only an occasional white blood cell. Indigo carmine appeared in the drainage in 5 minutes, although the phenolsulfonphthalein test and urea clearance tests indicated marked renal damage. Nephrostomy drainage averaged 45 ounces a day. The voided urine varied between 15 and 40 ounces a day. The weight was 81 pounds, the hemoglobin 70 per cent and the general condition was satisfactory.

COMMENT

The prognosis in the case presented remains guarded. She will probably be subject to pyelonephritic exacerbations. As long as adequate drainage is maintained, however, there is no reason why there should be any further kidney damage. Because of the late treatment, however, the function of the remaining kidney is poor. The possibility of removing the nephrostomy tube will be investigated again at a later date.

SUMMARY

A case of congenital bilateral hydronephrosis diagnosed late in the course of the disease with surgical therapy and complications is presented. The importance of early diagnosis is emphasized.

ACUTE PHLEGMONOUS CHOLECYSTITIS AS A COMPLICATION OF ACUTE APPENDICITIS

BORRIS A. KORNBLITH, M.D.

The experimental work with dogs by Rosenow (1) pointed to the close association of the gall-bladder, the appendix, the stomach and the pancreas as simultaneous foci of localization of infection. Subsequent clinical reports by Draper (2) and Carter (3) emphasized the reflex relationship between the gall-bladder and the appendix. A monograph by Heyd, Killian and MacNeal (4) further emphasized the coexistence of structural changes in the appendix, gall-bladder and liver in the same patient. They stated, "We are inclined to accept the idea of a relationship between appendicitis, hepatitis and cholecystitis in which it is assumed that the inflammation extends from the appendix to the liver through the portal vein or lymphatic system and thence to the gall-bladder, and from this point to the liver again and again during the repeated exacerbations of the cholecystitis."

All of the reports mentioned above dealt with mild involvement of the organs in question. The following case illustrates the association of the appendix and gall-bladder in a fulminating process in rapid succession. The fact that the complicating cholecystitis simulated the more common complications of appendicitis such as pylephlebitis, subphrenic or subhepatic abscess rendered the precise diagnosis difficult.

CASE REPORT

History. (Adm. 444756) I. R., a 41 year old white, very tall, asthenic male complained of severe abdominal pain of three days' duration. He had suffered from belching and moderate abdominal distress on several occasions during the past three years. He felt well otherwise. Thirty-six hours before admission to The Mount Sinai Hospital he took an overdose of castor oil because the abdominal pain was more severe on this occasion. There was no nausea or vomiting.

Examination. The patient appeared acutely ill. The temperature was 101.6°F., the pulse 84 per minute. There was exquisite tenderness in the right lower quadrant with involuntary rigidity and moderate rebound tenderness. The remainder of the abdomen was soft and non-tender. The rectal examination revealed marked tenderness on the right side. After the administration of morphine, a vague sensation of a mass was elicited by palpation in the right lower quadrant.

Operation. Under gas, oxygen and ether anesthesia, the abdomen was opened through a right lower rectus musele-splitting incision. The cecum was found fixed in the right lower quadrant, and could not be mobilized. There was a mass in the region of the appendix, which proved to be a small peri-appendiceal abscess. The appendix was mesoceeal and retro-cecal, markedly thickened and gangrenous, and had ruptured at the base. The appendix was removed. A purse-string suture of

Pagenstecher linen was placed at the base, thus closing the opening into the cecum. Three drains were put in place, one to the pelvis, another to the right lumbar gutter, and a third to the stump of the appendix. The abdomen was closed in layers, but the skin was paeked open.

Course. The temperature dropped to normal within a period of 48 hours. The drains were shortened and finally removed on the ninth day after operation. At that time the wound was irrigated with normal saline solution. The fascia sloughed praetically eompletely in the region of the wound. No fecal fistula developed. The patient's course was entirely uneventful until the twelfth day post-operatively when he complained of severe pain in his right lower chest. This pain was worse on respiration and was accompanied by a hacking cough. The temperature was 101°F., rising to 103°F. on the next day, accompanied by a respiratory rate of 32 per minute and moderate dyspnea. On examination, the respiratory excursions of the right ehest were noted to be diminished. There were dullness and diminished breath sounds in the right lower lobe region, but there were no râles or pleural frietion rub. The abdomen was held somewhat tensely. There was marked tenderness in the right upper quadrant and subcostally over the region of the gall-bladder. The remainder of the abdomen was soft.

Laboratory Data. The hemoglobin was 92 per cent; red blood cells 4,600,000; white blood cells 19,500; polynuclear lymphocytes 87 per cent, lymphocytes 7 per cent; monocytes 6 per cent. The urine examination was negative. A roentgenogram of the chest showed a moderate elevation of the right diaphragm. There was no evidence of pulmonary infiltration.

On the grounds that this patient might possibly have a pylephlebitis, sulfanilamide was given for two days (5). On September 2nd, 80 grains of sulfanilamide were administered in divided doses and on September 3rd, 60 grains in divided doses. Repeated blood counts revealed no evidence of agranulocytosis. The patient's temperature dropped from 104°F. to between 101°F. and 102°F. The pain in his right upper quadrant lessened. The signs in his chest diminished and he was much more comfortable, but he developed an icterus.

Laboratory Data. The urine was 3 plus positive for bile. Blood eounts were as follows: September 3, 1939, hemoglobin 90 per cent; red blood cells 4.5 million; white blood cells 27,500; polymorphonuclears 81 per cent; lymphocytes 19 per cent. September 5, 1939, hemoglobin 75 per cent; red blood cells 4.0 million; white blood cells 16,500; polymorphonuclears 79 per cent; lymphocytes 13 per cent and monocytes 8 per cent.

In view of the fact that the abdominal signs did not subside, laparotomy was decided upon. The pre-operative diagnosis of a possible subhepatic abscess, or an acute cholecystitis was entertained. The patient had been under observation for 4 days. The physical signs all pointed anteriorly, to the subcostal region.

Operation. Under ethylene anesthesia a subcostal incision in the right upper quadrant was made. The reetus sheath was edematous and thickened. The fundus of the gall-bladder was gangrenous and markedly adherent to the peritoneum. The right lobe of the liver was covered by fibrino-purulent exudate. The entire liver was swollen. After packing off the viscera, the gall-bladder opened and drained off about 200 cc. of brown purulent material. The entire mucosa and submucosa were necrotic and sloughing. There were no calculi. A clamp was introduced into the gall-bladder to remove some of the slough and succeeded in enueleating practically the entire mucosa and submucosa, leaving a moderately thickened, inflamed shell of museularis and serosa. Cholecystostomy was performed using a large rubber tube. Four gauze packings were placed around the gall-bladder and a rubber dam drain to the upper surface of the right lobe of the liver.

Course. Twenty-four hours after operation the eholecystostomy drained a large quantity of bile. The wound was kept clean by means of suetion through the chole-

cystostomy tube and the application of aluminum paste around the wound edges. 3000 cc. of 5 per cent glucose in normal saline was administered intravenously for a period of twenty-four hours, and 50 cc. of 50 per cent glucose, three times daily for five days. The stools were at no time clay-colored and the patient's jaundice promptly disappeared within four days after the operation. The wound began to heal by granulation. Biliary drainage from the gall-bladder ceased after twenty-eight days. The patient was then discharged from the hospital with both abdominal wounds healing.

He was observed over a period of ten months post-operatively. Both wounds were completely healed, and the patient was asymptomatic.

DISCUSSION

It is probable that the acute appendicitis and the acute cholecystitis in this particular case were not coincidental but rather associated lesions for the following reasons: First, there was no previous history of cholecystitis. Also, no calculi were found in the gall-bladder as evidence of previous disease when cholecystostomy was performed.

When sulfanilamide was given the patient's symptoms improved, his temperature fell at least two degrees and the abdominal signs likewise became less marked. However, he became jaundiced after 140 grains of the drug. In this particular case this drug served to confuse the picture and was of doubtful value. It is difficult to decide which produced the jaundice, the sulfanilamide or the existing hepatitis. The course of the phlegmonous cholecystitis was, nevertheless, not altered. The decision to operate rested upon the physical findings which, fortunately, were not too much obscured.

SUMMARY

1. A case of acute phlegmonous cholecystitis as a complication of acute appendicitis is presented.

2. The sequence of events suggests a direct etiological connection between the two surgical conditions, rather than a mere coincidental relationship.

3. This complication is unusual. In this case it was difficult to differentiate it from pylephlebitis, liver abscess, subphrenic or subhepatic abscess and pulmonary infarction of the right lower lobe.

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HABITUAL LUXATION OF THE ULNAR NERVE

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Habitual luxation of the ulnar nerve may be defined as a condition in which the ulnar nerve slips anteriorly over the internal epicondyle of the humerus when the elbow is flexed, and returns again to the epitrochlear-olecranon groove when the extremity is extended. It may be divided into two types:

1. Traumatic, in which habitual luxation occurs in a previously normal elbow as a result of an injury—usually a contusion of the inner side of the elbow—which presumably tears the fascia overlying the retro-epitrochlear groove.

2. Non-traumatic, in which the luxation is not due to an obvious trauma but is insidious in onset and often unnoticed until the development of neuritic symptoms. Cases of congenital origin, those associated with deformities of the elbow (such as cubitus varus, or posterior position of the medial epicondyle—as in the recent report of Berman and Sutro (1)), and those of unknown etiology all fall into this classification.

Habitual dislocation of the ulnar nerve was first reported by Blattman (2) in 1851. The first operation was done by Poncet (3) in 1888. Thereafter, case reports followed rapidly until Jopson (4) in 1898 was able to collect sixteen traumatic and ten non-traumatic cases, with seven operations, to which he himself added two cases, one traumatic case on which he had operated, and one non-traumatic case.

Cobb (5) reported a case in 1903 and analyzed fifteen previously published operated cases, in all but one of which the nerve had been replaced in the retro-epitrochlear groove.

Dubs (6) in 1918, reviewed all the previous literature and found seventy cases of ulnar luxation, of which twenty-seven were indubitably traumatic. He added three traumatic cases of his own. His article is of interest in that it mentions the collected statistics of Ramonenq, Collinet, Drouard, Kissinger, Cobb, Haim, and Momberg in relation to the proportion of hypermobile ulnar nerves in normal elbows. In the aggregate these show forty-three cases of congenital (non-traumatic) luxation in 1,816 cases, an incidence of 2 per cent.

Cases of traumatic luxation were subsequently published by Duchamp (7) (1924), and Sarroste and Reberal (8) (1934). In 1925 Platt (9) published an excellent article concerning affections of the ulnar nerve,

in which he reported six cases of ulnar luxation of which two were clearly traumatic (following contusion).

Platt emphasized the operation of anterior transposition, in contradistinction to the practise of replacing the nerve behind the epicondyle, which had been done in the great majority of cases up to his time. This operation was first performed by Roux, but the result was disappointing as the nerve had been transplanted subcutaneously.

Medical experience in the World War afforded a wealth of material and, as a result, the technique of ulnar transposition became standardized, the one essential feature being the deep imbedding of the nerve in an intramuscular plane.

Platt believes that if no signs of neuritis are present, conservative methods of treatment should be tried first, unless there are strong economic reasons for urging early operation. If symptoms of ulnar neuritis are present, the operation should not be delayed.

In the operative technique, he emphasizes that: (1) the nerve must be generously freed in the lower arm and upper forearm; (2) the fine filament to the elbow joint may be sacrificed, but great care must be taken to conserve the branches to the flexor carpi ulnaris and flexor digitorum profundus muscles, which arise in the lower part of the ulnar groove; (3) the nerve bed must be situated in an intramuscular plane by division of superficial fibers of the flexors taking origin from the internal epicondyle; (4) where the nerve trunk passes the intermuscular septum of the arm, this latter structure must be adequately resected so as to prevent tension.

CASE REPORT

History. (Adm. 445109) E. G., a 16 year old white male student, was admitted to the hospital on August 8, 1939 with the complaint of a "slipping" sensation in the left elbow for two weeks.

The family history and past history were irrelevant. The patient had always been in good general health.

Two weeks before the date of admission, the patient was struck across the inner side of his left elbow. The ulnar side of the forearm and the ulnar two fingers immediately became numb and the patient noticed a "tingling" sensation in this region. Numbness and paresthesias in the ulnar nerve distribution persisted for fifteen minutes, then gradually disappeared. Since that time, however, the patient had noted that a "cord" slipped anteriorly across the internal humeral epicondyle each time he flexed his elbow, and slipped back again with extension. This slipping was not accompanied by any pain or paresthesias in the ulnar distribution. The elbow was strapped in extension for several days by his family physician in an effort to secure permanent replacement, but without success.

Examination. The patient was a well-developed and well-nourished white male in obviously excellent health. He was large for his age and well-muscled. Examination was negative, save for the local condition. Both elbows were symmetrical. There was no bony abnormality, no cubitus varus or valgus. In extension, the left ulnar nerve was in its proper position behind the epicondyle, but as the elbow was flexed it became visible as a taut cord in the lower arm, and at about 150 degrees the nerve suddenly slipped anteriorly over the epicondyle and came to lie in front of it

(fig. 1). The nerve slipped back into place as the elbow was extended. No motor or sensory disturbance in the ulnar distribution was detected by a careful neurological examination.

It was felt that in view of the simplicity and efficiency of the operation of anterior transplantation of the nerve, the necessarily long period of conservative therapy was not warranted, especially in a young, active individual. Hence, on September 2, 1939 the patient was operated on by the following technique:

Operation (Gas, oxygen, ether anesthesia). The skin was divided by a semicurved incision anterior to the medial epicondyle of the humerus with the convexity anteriorly. The elbow was then flexed, bringing the nerve anteriorly into the area

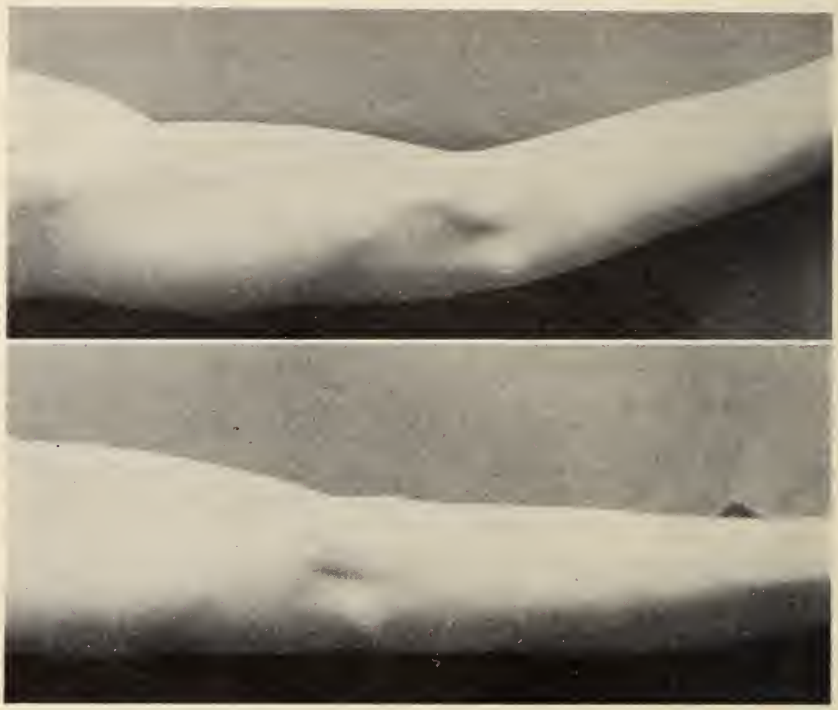

FIG. 1 (Upper). The ridge in the skin marking the course of the ulnar nerve is anterior to the internal epicondyle when the elbow is flexed 15°–20°.

FIG. 2 (Lower). The ulnar nerve slips back posteriorly in full extension of the elbow, as marked by the change in position of the ridge in the skin.

of the incision. The overlying soft tissues were then divided and the nerve isolated. The nerve was apparently normal, there being no thickening or evidence of neuroma. However, a small portion of the sheath was stained with blood pigment which may have been a residual evidence of the recent trauma.

While the nerve was retracted from the operative field with saline tapes, a groove one-half inch deep was cut in the substance of the muscles arising from the internal epicondyle. The nerve was then inserted into this groove and the overlying fascia of the muscle sutured over it loosely.

It was found to lie comfortably in the groove in extension and flexion of the elbow. The intermuscular septa were carefully divided at the level of the groove where necessary so that no pressure would be made upon the nerve. The soft tissues were

closed in layers with interrupted, buried catgut sutures, and a continuous silk suture for skin. The elbow was put up in a voluminous dressing at an angle of 120 degrees.

Course. The postoperative course was uneventful. Nerve status was tested immediately postoperatively and later at intervals and no evidence of any sensory or motor impairment was found. The patient was discharged on September 9, 1939 to his private physician.

He returned to the Follow-Up Clinic on September 28, 1939, when the nerve status was again determined and found intact. The scar was well-healed, not painful or tender. The nerve maintained its anterior position in all positions of the elbow.

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REPORT OF A BRUNNER GLAND ADENOMA OF THE DUODENUM DISCOVERED INCIDENTALLY AT AUTOPSY

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The occurrence of benign duodenal tumors, in general, and of Brunner gland adenomata of the duodenum, in particular, is rare. During the past twelve years, not a single Brunner gland adenoma was found in a series of 5,643 autopsies performed at The Mount Sinai Hospital. A survey of the literature revealed 15 authors who described adenomata of Brunner's glands. In Cruveilhier's report (1) a sessile, mammillated tumor, the size of a walnut, was described, the exact location not being indicated. Salvioli (4) described a tumor 2.2 cm. in diameter composed of Brunner's glands, the exact location being omitted. Versé (5) reported a case in which two adenomata were found in the duodenum, one being 1 x 1.5 cm. on the posterior wall 3 cm. from the pylorus, and the second 0.7 cm. in diameter found 5 cm. from the pylorus and 2 cm. from the papilla of Vater. Both were composed of Brunner's glands (other polypi of cecum, colon and rectum were associated with those of the duodenum). Weishaupt (6) described a pea-sized Brunner gland adenoma on the posterior wall of the duodenum just beyond the pyloric sphincter in an infant eleven days old. At the level of its attachment, the circular muscle of the duodenum was much hypertrophied, producing a narrowing of the lumen. Scagliosi (7) described a polyp 1.5 cm. in diameter on the posterior duodenal wall adjacent to the papilla of Vater. This polyp proved to be an adenoma of Brunner's glands which had in part undergone malignant changes. The patient was exsanguinated due to repeated hemorrhages from an eroded vessel at the summit of this tumor. Willis and Lasersohn (8) removed a 3.5 x 3 x 2 cm. polyp, which was attached to the posterior wall of the duodenum 2.5 cm. from the pyloric sphincter, from a patient suffering from epigastric pain and nausea. Golden (3) in a review of this subject added a case of his own, reporting a patient who suffered from epigastric distress for about five years and who on X-ray examination, revealed a filling defect in the first part of the duodenum, which was diagnosed as a polyp. At operation, a polyp 1 x 0.5 cm. was found on the anterior surface of the first portion of the duodenum. Histologically there was an adenomatous hyperplasia of Brunner's glands beneath the muscularis mucosa. Kellog (9) reported a case of intussusception of the first portion of the duodenum and pyloric end of the stomach into the jejunum with incom-

plete obstruction caused by a polyp attached to the posterior wall of the duodenum close to the pyloric ring. The tumor was 6 cm. in diameter and partially covered by duodenal mucosa. The entire tumor was made up of Brunner gland acini. Kellog (9) referred to a case reported by de Rouville and Martin (10) where a polyp composed of Brunner glands caused the death of a patient by ulceration and perforation of the duodenal wall. An interesting case was the one reported by Pavel and Milian (11) where in an autopsy case "miliary polypi" of Brunner's glands, the largest being the size of a cherry stone, were found throughout the mucosal surface of the duodenum stopping 1 to 2 cm. from the pyloric sphincter. Feyrter (12) studied the duodenum of 3400 consecutive autopsies and found three cases of single duodenal adenomata composed of Brunner's glands (.12 per cent). This author gave a detailed histological description of these adenomata. Other isolated cases of adenomata of Brunner's glands were reported by Balfour and Henderson (2); Oberndorfer (12); Sworn and Minton (14) and Reeves and Golden (15).

In summary, only 17 cases of Brunner gland adenomata have been described varying in size from 1 to 2 mm. to 7 cm. in diameter. They have been found in the first and second portions of the duodenum from immediately beyond the pyloric sphincter to the lower portion of the descending duodenum. Most reports have located the adenomata on the posterior wall of the duodenum.

Because of the unusual finding of Brunner gland adenomata at autopsy, the following case report is presented.

CASE REPORT

History. (Adm. 445536) A 59 year old man entered the hospital on September 7, 1939. His clinical history revealed that for seventeen years up until 1932 he had suffered from attacks of "stomach trouble" consisting of gaseous eructations with an acid taste, epigastric discomfort and pain which was relieved by bicarbonate of soda but not by food. The patient experienced, in addition, fairly frequent spells of nausea and vomiting. There was no history of tarry stools, weight loss or anemia. Roentgenographic studies were not done. The patient died four days after admission to the hospital. The clinical diagnosis was: chronic pulmonary emphysema, chronic bronchitis and bronchiolitis, focal acute and chronic bronchopneumonia and generalized arteriosclerosis.

Necropsy Findings. There was found on the posterior wall of the duodenum just beyond the pyloric ring, a firm, smooth gray-tan polyp, completely covered by duodenal mucosa. It measured 1 x 1.3 x 1.5 cm. and was attached to the mucosa of the pyloric ring by a broad pedicle measuring 8 x 7 mm. The polyp was freely movable, and projected into the lumen of the duodenum, where there was a free space of 1 cm. between the summit of the polyp and the duodenal wall. On section, the polyp was seen to be composed of small lobules which were homogeneous in appearance, yellow-tan in color, and which looked as if they could be shelled out (fig. 1). An associated finding was a small depressed area on the anterior wall of the stomach measuring 1 cm. in diameter, which slightly thickened and diminished the pliability of the stomach wall at this point. Microscopic examination of this area showed an old, healed peptic ulcer with conspicuous thickening of the muscularis mucosa and

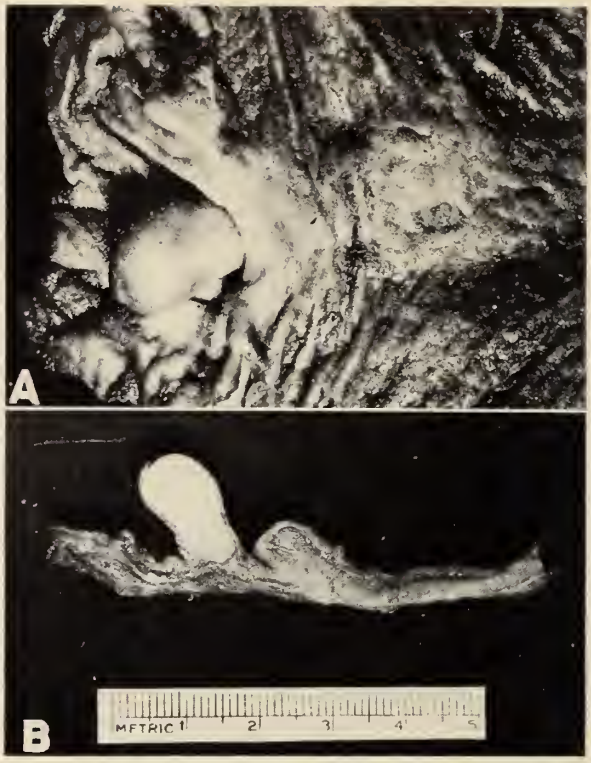

FIG. 1. (A) The Brunner gland adenomatous polyp arises from the pyloric ring on the posterior aspect of the duodenal wall. (B) Sagittal section—note sharp circumscription with homogeneity of structure.

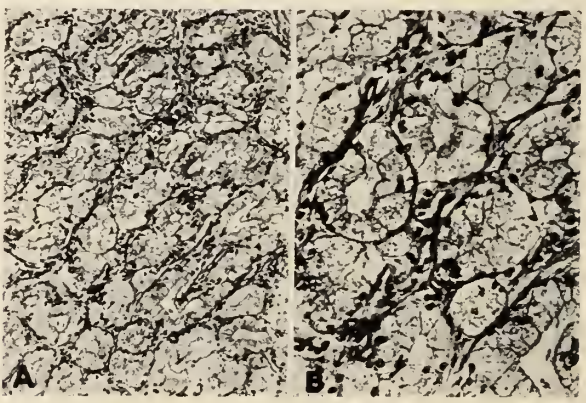

FIG. 2. (A) The adenoma is seen to consist of glandular acini under low power. (B) Higher magnification—note the characteristic appearance of Brunner glands (hematoxylin and eosin).

submucosal fibrosis. An artery in this section showed marked arteriosclerotic thickening and narrowing of the lumen.

A section of the polyp stained with hematoxylin and eosin (fig. 2) showed on microscopic examination with the low power objective, a circumscribed nodule composed of gland acini situated between the muscularis mucosa and the muscle layers of the duodenal wall. This adenomatous nodule compressed and thinned out the overlying mucosa and the muscle layers of the duodenum directly beneath it. The duodenal mucosa overlying the adenoma was intact. Examination with the higher power objective showed the muscularis mucosa to be infiltrated by lymphocytes and plasma cells, and more dense collections of lymphocytes were found in certain areas of the submucosa. The adenomatous hyperplasia of glands seen with the low power had the characteristic appearance of Brunner's glands. The cells were pale, contained pink-staining granular material in a vacuolated cytoplasm with darkly staining, basally placed nuclei, and were arranged in acini. No cell atypism could be found. The interacinar tissue was delicate and collagenous in character. The interlobular septa were thicker and in some areas contained collections of lymphocytes. Toward the mucosal surface of the section and embedded in a connective tissue stroma heavily infiltrated with lymphocytes, were several dilated ducts filled with pink, granular material and desquamated cells.

COMMENT

The microscopic appearance of the polyp found in this case, corresponded precisely with the single duodenal adenomata described by Feyrter (12) and by other authors who have described and illustrated their findings of single adenoma of Brunner's glands (3, 11, 9, 14). Feyrter described the isolated adenoma as being a local hyperplasia of Brunner's glands, varying in size from pea-sized to nut-sized, rounded but not encapsulated and arising in Brunner's glands below the muscularis mucosae. The lumen of the glands and ducts were filled with inspissated secretion. Paneth cells were not found and, as a rule, the Brunner glands in the rest of the duodenum were atrophic, a finding which was not present in the case reported.

Such adenomata may give rise to clinical manifestations under certain conditions. An adenoma of sufficient size strategically situated near the pyloric ring can give rise to intestinal obstruction. Ulceration of the mucosal surface of such adenomata may cause intestinal bleeding of varying severity. X-ray examination may reveal a filling defect in the involved portion of the duodenum.

It is believed that in the case reported the gastric ulcer which had healed was most probably responsible for the patient's early gastric symptoms, and that the Brunner gland adenoma found in the duodenum was an incidental finding. This conception is supported by the fact that the patient was free of gastro-intestinal symptoms for seven years before his death.

SUMMARY

1. A rare case of Brunner gland adenoma of the duodenum is described.

2. Seventeen cases of Brunner gland adenomata described in the literature are reviewed.

3. Possible clinical manifestations have been suggested, although in the case reported, the Brunner gland adenoma was an incidental finding.

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RADIOLOGY AND RADIOTHERAPY COMBINED CONFERENCE

MARCY L. SUSSMAN, M.D., *presiding*

January 4, 1940

[*Cases presented from the Department of Radiology*]

Case 3.[1] Probable Parathyroid Tumor With Renal Insufficiency

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

History. (Adm. 371839). A 55 year old white female was admitted to the hospital on November 16, 1932, complaining of lumbar pain, urinary frequency, nocturia, anorexia and nausea of ten days' duration. She recalled that in 1922 she had had lumbar pain and frequency.

Examination. There were no significant abnormalities other than a palpable left kidney. The blood pressure was 166 systolic and 90 diastolic.

Laboratory Data. The blood hemoglobin was 74 per cent; white blood cells were 6000; the blood Wassermann reaction was negative, the blood urea nitrogen was 20 and the blood sugar was 100 milligrams per cent. The urine contained traces of albumin, was loaded with clumped white blood cells and a few red blood cells.

Course. The patient was discharged after a few days of observation. No roentgenograms were taken. The discharge diagnosis was "Lumbar pain of unknown origin and Psychoneurosis."

Second Admission. The patient was admitted on October 6, 1934 with a history of an upper respiratory infection, and pain in the chest for five days with a temperature up to 102.4°F.

Examination. There were physical signs of pneumonia in the left lung. Both right and left kidneys were palpable.

Laboratory Data. The blood hemoglobin was 90 per cent, white blood cells were 9600 with a normal differential count. The sputum was negative for tubercle bacilli. Urinary concentration tests showed the highest specific gravity to be 1015; there was 20 per cent excretion of phenolsulphonephthalein in four hours. The blood calcium determinations varied from 11.4 to 12.5 and the blood phosphorus from 3.2 to 3.7 milligrams per cent within an interval of about one week. The blood urea nitrogen was 44.0 and the blood sugar 105 milligrams per cent. X-ray examination of the abdomen revealed bilateral dendritic calculi. The urine showed a moderate albuminuria and was loaded with pus cells. The blood Wassermann reaction was negative.

Course. In the hospital, the temperature slowly dropped to normal. Cystoscopy and further genito-urinary examinations were refused. The patient was discharged to the Follow-Up clinic which she attended irregularly.

Third Admission. The patient was admitted on November 21, 1939, with a history of gross hematuria and pain in the left flank noted 3 weeks previously. She related that in 1938 she noted a painless mass in the right flank and shortly thereafter,

[1] The first two cases were presented in a previous issue of the Journal (Vol. VII, No. 3).

a smaller one in the left flank. Since 1937, there had been moderate dyspnea and slight precordial pain on exertion.

Examination. The heart was enlarged to the left and systolic murmurs were heard over the apex and over the aortic area. Bilateral non-tender masses were palpated in the flanks. The blood pressure was 190 systolic and 100 diastolic.

FIG. 6. Case 3. Miliary decalcification of the skull with small areas of sclerosis.

FIG. 7

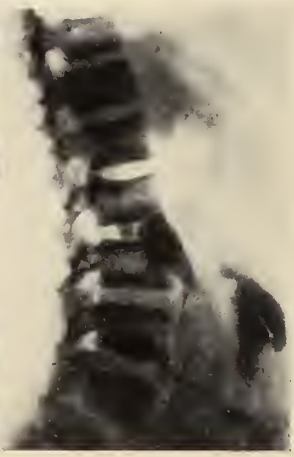

FIG. 8

FIG. 7. Case 3. Sclerosis of the dorsal vertebral bodies particularly at the periphery of the bodies.

FIG. 8. Case 3. Similar changes in the lumbar vertebrae, bilateral renal calculi, and calcification of the abdominal aorta are seen.

Laboratory Data. The blood hemoglobin was 45 per cent; white blood cells were 7500 with a normal differential count. The blood calcium was 11.0 and phosphorus 4.5 milligrams per cent. The serum phosphatase was 44.0 King-Armstrong units per 100 cubic centimeters of blood. Cystoscopic examination revealed a marked

impairment of kidney function of both sides. X-ray examination of the skull showed changes suggestive of osteitis fibrosa.

Course. On December 2, 1939, exploration of the neck was done. The thyroid gland was enlarged to about three times its normal size. Only one parathyroid which appeared normal was identified. No parathyroid adenoma was found. Ten days later, a left nephrolithotomy and nephrostomy were done. It was felt at this time that considerable improvement in her general condition would have to occur before mediastinal exploration could be undertaken.

Comment: Dr. M. L. Sussman. Roentgenograms of the skull showed a diffuse miliary decalcification of the calvarium with small areas of increased density presumably due to sclerosis. The entire spine and pelvis showed similar changes. The vertebral bodies, particularly, showed increased density at their articular margins without increase in the size of the bones. The long bones showed slight decalcification. There was marked calcification of the vessels throughout the body even in the axillary and cerebral areas. There was also calcification of the semi-lunar cartilages of the knees. Hence, in spite of the fact that a parathyroid adenoma was not identified at operation, this appears to be the most likely diagnosis. The elevation of the blood phosphorus may be due to renal insufficiency.

Reported by *N. Rudner, M.D.*

Case 4. Osteitis Fibrosa Cystica With Probable Hyperparathyroidism

[*From the Gynecological Service of Dr. Samuel Geist*]

History. (Adm. 429907). A white female, single, aged 26 was admitted to the hospital on September 21, 1938 with a complaint of amenorrhea of three months duration. She had been in excellent health until eight years before admission when, following several episodes of right costovertebral pain and urinary difficulty, a diagnosis of right kidney stone was made and a right pyelolithotomy was performed. Seven years before admission she fractured the upper end of the right humerus which necessitated an open reduction. At that time X-ray and blood chemical studies revealed the possible presence of osteitis fibrosa cystica due to hyperparathyroidism. From May, 1931 until March, 1938 she was followed closely at another institution. Roentgenograms of the skeletal system revealed cyst formation in the head of the right humerus, the left scapula, the iliac bones, the right femur and the left jaw. For the most part, the findings remained more or less constant. The blood calcium was consistently high and blood phosphorus was low while the phosphatase was slightly elevated. Biopsy and pathological examination of a fragment of rib showed "osteitis fibrosa cystica." In September, 1935 an exploration of the neck was performed for parathyroid tumor. The right inferior parathyroid gland was removed and microscopically was found to contain "well vascularized fat tissue." Following the operation her condition remained unchanged. Three

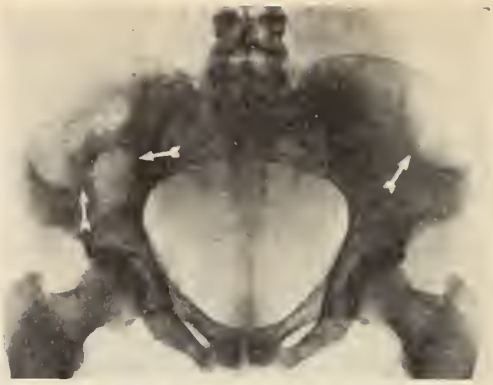

FIG. 9. Case 4. Large cystic areas are demonstrated in both ossa innominata.

FIG. 10. Case 4. Left mandible showing an epulis with almost complete destruction of the mandible.

FIG. 11. Case 4. The skull shows thickening of all the bones with peculiar alternation of rarefaction and opacity which usually suggests Paget's disease.

months before admission she missed a menstrual period and had not menstruated since. She was considered pregnant and was referred into the hospital for a therapeutic abortion.

Examination. The patient appeared to be somewhat undernourished and chronically ill. The blood pressure was 98 systolic and 60 diastolic. Aside from old healed operative scars on the trunk, extremities and neck, the physical findings were not abnormal except in the pelvis where a positive Hegar sign was elicited and the uterus was felt to be the size of a three and one half month pregnancy.

Laboratory Data. The hemoglobin was 72 per cent; the white blood cell count 9,800 per cu. mm. with a normal differential count. The blood Wassermann reaction was negative. The Aschheim-Zondek test performed on the urine was positive. The urine showed no abnormalities except for the presence of an occasional white blood cell and many phosphate casts in the sediment. The blood calcium was

TABLE 1

Summary of laboratory blood findings

DATE	BLOOD Ca	BLOOD P	PHOS-PHAT.	SER. ALB.	SER. GLOB.	TOT. PROT.	UREA N	
	mgm. %	*mgm. %*	*K-A units*	*mgm. %*	*mgm. %*	*mgm. %*	*mgm. %*	
9/11/35	11.8	2.3	20.0					Prior to 1st neck exploration
9/13/35	14.0	1.7	24.0			6.35		
5/28/36	12.0	2.6	4.5					Observation at St. Lukes Hospital
3/24/37	13.1	2.3	19.5			6.5	16.2	
6/ 3/38	13.3	2.2	5.2					
9/22/38	11.0	2.4	90.0				8.0	Prior to abortion
9/26/38	11.9	2.6		4.3	0.9	5.2	7.0	
10/6/38	14.4	2.7	64.5	3.3	1.7	5.0		After abortion. Before second neck exploration
6/21/39	12.4	3.1	85.0	5.4	1.0	6.4	13.0	

elevated, the phosphorus low and the phosphatase markedly elevated (see Chart 2). The Hamilton-Highman test for parathormone in the blood was negative. On an intake of 100 mg. of calcium per day there was an excretion of 431 mg. of calcium indicating a markedly negative balance.

Course. Eight days after admission an abdominal hysterotomy and tubal ligation were performed. The patient was delivered of a well-formed 14-week old fetus which on examination proved to be perfectly normal. The post-operative course was uneventful and the patient was discharged three weeks after admission.

Second Admission. The patient was admitted on June 20, 1939 for exploration of the neck after having been followed for about nine months in the Out-Patient Department. Her only complaint was easy fatiguability. The physical examination at this time revealed no abnormalities.

Laboratory Data. The blood chemical findings were unchanged. The urine showed 3 plus albumin, absence of sugar and a few white cells in the sediment. A subsequent urine examination revealed no albumin. The specific gravity of the urine was as high as 1.026. The phenolsulphonphthalein excretion was normal.

Course. Two days after admission exploration of the neck was performed. The remaining three parathyroid glands were found to be normal with no evidence of tumor. The post-operative course was uneventful and she was discharged four days later to the Follow-Up clinic with recommendation for exploration of the anterior mediastinum at a later date. The patient has failed to report since discharge to the clinic and her whereabouts are unknown.

The clinical diagnosis remains hyperparathyroidism with osteitis fibrosa cystica, in spite of the fact that one normal parathyroid gland has been removed and three other normal glands have been identified. (*This case has already been published in detail in the J. A. M. A. 113, 1939.*)

Comment: Dr. M. L. Sussman. This case has been described completely in a recent publication from this Hospital. It is unnecessary to repeat the admirable discussion presented in this paper. The case is included in the present group because of the large cyst formation with relatively mild decalcification of the skeleton. The skull, on the other hand, showed marked thickening of the bones of the calvarium. There was moderate diffuse decalcification with small areas of opacity which, considered without the remainder of the skeleton, would be difficult to differentiate from Paget's Disease.

Reported by *Harold G. Jacobson, M.D.*

CLINICAL PATHOLOGICAL CONFERENCE

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

Wednesday, October 18, 1939

Agranulocytosis Due to Sulfanilamide Therapy in a Case of Subacute Bacterial Endocarditis

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

History (Adm. 437431; P.M. 11129). This was the first admission of a nineteen year old female college student who, eight years before, on routine examination, was found to have rheumatic heart disease. She had never had any symptoms, even on exercise; there were no symptoms of diminished cardiac reserve. During the two months preceding admission, she had several tender, painful lesions on the feet and thighs for five days. One month before admission she noted a decrease in appetite and ready fatigability. Ten days before admission her physician found fever and anemia to be present. Bed rest was enforced and the temperature was found to have a daily rise to 101 to 102°F.; new tender skin lesions continued to appear.

Examination. The patient was a well-developed and well-nourished girl who appeared somewhat pale. Temperature was 102.4°F. The lungs were clear. The heart was enlarged to the left; the apical impulse was forceful; the first apical sound was markedly accentuated and was followed by a loud, rough systolic murmur; A2 was greater than P2. Blood pressure was 120 systolic and 85 diastolic. The spleen was not palpable. On both hands there were four or five non-tender irregular hemorrhagic areas 2 to 3 millimeters in size which did not blanch on pressure. Several irregular pinkish areas were seen on the soles of the feet. No clubbing was present. Rheumatic heart disease; mitral stenosis and insufficiency; subacute bacterial endocarditis were considered as probable diagnoses.

Laboratory Data. The hemoglobin, 60 per cent; red blood cells, 3,200,000; white blood cells, 9,600 (63 per cent segmented and 17 per cent non-segmented polymorphonuclear leucocytes; 13 per cent lymphocytes; 7 per cent monocytes). The urine showed a faint trace of albumin and 2 to 3 red blood cells and occasional white blood cells per high power field. The blood Wassermann reaction was negative. Blood chemistry was normal. Blood culture revealed 10 colonies per cubic centimeter of Streptococcus viridans alpha. Electrocardiogram revealed sinus tachycardia, and a P-R interval of 0.24 seconds.

Course. The patient ran a febrile course. Showers of embolic lesions continued to appear. Small numbers of red cells continued to be present in the urine. In an attempt to cure the underlying pathology, she was treated with large doses of sulfanilamide, as well as three hyperthermia treatments. At first 6 grams of the drug were given daily; this dose was later increased to 8 grams daily. At the end of three weeks she had received a total of 146 grams. At the end of this period there was only

one colony of Streptococcus viridans per cubic centimeter in the blood culture. The blood picture, however, disclosed dramatic changes. One week after the initiation of the sulfanilamide therapy the hemoglobin was 60 per cent and the white blood cell count, 12,200; on the twelfth day, 8,200; on the twentieth day, 1150; on the twenty-first day the hemoglobin was 49 per cent and the white cell count had fallen to 1,000 cells per cubic millimeter (94 per cent lymphocytes, 6 per cent monocytes and complete absence of any granulocytes). A blood sulfanilamide determination at this time revealed a concentration of 6.1 mg. per 100 cc. To combat the agranulocytosis the patient was given several transfusions, and injections of liver extract. The administration of sulfanilamide was discontinued. Nevertheless, the white count continued to fall to 700 cells per cubic millimeter, with a lymphocyte ratio of 97 per cent and continued complete absence of granulocytes. The bone marrow showed a fairly active hematopoiesis, but the great majority of the cells were of the erythroid series. At this time the patient began to complain of soreness of the throat. The throat, on examination, was only slightly reddened. However, there was rapid progression so that there was soon present over the fauces, tonsils, pharynx and soft palate numerous white circular patches surrounded by a zone of erythema. The temperature rose rapidly to 104 to 105°F., which persisted. In spite of the treatment, the patient grew progressively worse and died four days after the detection of the agranulocytosis.

Necropsy Findings. The *heart* showed rheumatic involvement of the left auricle and the mitral valve. Just above the posterior mitral leaflet was a typical MacCallum lesion which was uninvolved by bacterial endocarditis. The posterior cusp of the mitral valve showed distinctly thickened and shortened chordae. The only lesion of subacute bacterial endocarditis was confined to the anterior mitral cusp and consisted of small nodular vegetations. Microscopically these lesions still showed the presence of bacteria, but there was a striking proliferation of fibroblasts within the vegetations. Infarcts were demonstrable in the *kidney* and *spleen*. The former viscus showed embolic closure of some of the smaller vessels, with many bacteria in the occluding emboli.

The pathological evidences of agranulocytosis were evident in many organs. The *bone marrow* showed a striking reduction in the number of cells, affecting chiefly the granulocytes; there was an absence of polymorphonuclear leucocytes and only very few myelocytes, whereas the number of red cells and megakaryocytes were normal. The *intestine* revealed definite areas of necrosis, particularly in the terminal ileum, the cecum, and one large area of necrosis in the rectum. The *lungs* showed a very red, diffuse pneumonia, such as is commonly found in agranulocytosis because of the lack of emigrating leucocytes.

Comment. Dr. Klemperer. The interesting feature in this case is the definite tendency towards healing and fibrosis that is present in the bacterial vegetation on the heart valve. Although this is suggestive of a beneficial therapeutic effect attendant upon the use of sulfanilamide, it must be borne in mind that previous to the use of this chemical, similar cases were encountered occasionally.

Dr. Baehr. The lesson to be learned from this case is that white blood counts and differential counts should be made at least every other day (preferably daily) while sulfanilamide or sulfapyridine is being administered. It is especially unfortunate in view of the evidence of healing of the vegetations, that the patient succumbed to granulopenia, as a successful therapeutic result may well have been achieved. When granulopenia

begins, the discontinuance of therapy often results in prompt recovery. Recovery can not be expected if discovery of granulopenia is not made until all the polymorphonuclear leucocytes have vanished from the circulating blood. In watching for granulopenia, the differential count is even more important than the total white count, since the former often shows the earliest changes. Granulopenia is a much better term than agranulocytosis, since it emphasizes the importance of early detection of impending disaster, thus permitting earlier discontinuance of the offending drug.

Dr. Ottenberg. It is certainly wise to take frequent blood counts. However, it should be mentioned that merely stopping the drug will not always prevent a fatal issue. I have seen two cases of granulopenia due to sulfapyridine where the evidence of bone marrow damage first made its appearance after the drug had been stopped. In other words, the damage to the bone marrow had already been done.

Dr. Baehr. I would reiterate that no one would wish to continue the administration of an offending drug after the onset of granulopenia. The continued ingestion of the drug after the onset of evidences of granulopenia must prejudice the patient's chances of recovery.

Teratoma of Anterior Mediastinum with Carcinomatous Transformation. Suppurative Pericarditis

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

History. (Adm. 438718; P.M. 11169) This patient, a female thirty-three years old, was first seen in this hospital fourteen years ago complaining of pain in the chest and cough of three years duration. X-ray examination at that time reported a "tumor in the chest" most likely of pleural origin. Since her discharge she continued to have a mild chronic productive cough which during the past two years had increased to about a half glass of greenish non-foul smelling sputum a day. There had been occasional slight blood streaking of sputum, but no gross hemoptysis. Two days before her admission to the hospital she experienced a sudden sharp pain in the left lower chest anteriorly, accompanied by a temperature rise to 104°F. There was no chill, but she noticed that from then to entry, she ceased to expectorate. She claimed that she did not expectorate because it hurt her too much to cough. The temperature remained between 100° and 103°F. with continuance of pain and a dry cough to entry. There had been no recent weight loss.

Examination. The patient was a well developed young adult, moderately dyspneic, with pain in the lower left chest aggravated by cough. Her tongue was dry. The entire right chest was somewhat flattened and moved less than the left on respiration. On the right there was dulness to flatness over the entire right lung anteriorly and posteriorly below the third interspace with flatness at the extreme

posterior base. The breath sounds in these areas were diminished to absent, and there were occasional coarse râles at the lower portion of the left lung in the mid-axillary line. The fingers and toes were moderately clubbed. The clinical impression was bronchiectasis and fibrosis of the right middle lobe with a question of amyloidosis.

Laboratory Data. The blood hemoglobin was 73 per cent (Sahli). The blood pressure was 100 systolic and 70 diastolic. The urine had a high specific gravity with 2 plus albumin and occasional granular casts and white blood cells. X-ray examination of the chest showed a fairly homogeneous shadow occupying the lower half of the right lung. In the region of the right middle lobe there were small calcific areas resembling bronchioliths. It was felt that the right middle lobe was atelectatic and that a small pericardial effusion was also present.

Course. On the evening following admission she suddenly went into collapse, and her blood pressure fell to 80 systolic and 60 diastolic. The pulse rate rose to 130 per minute and the venous pressure taken a few hours later was 24.5 cm. of water. This was associated with a temperature rise to 103°F. X-ray studies revealed the presence of a pericardial effusion. Aspiration of the pericardium revealed the presence of large quantities of turbid fluid from which pneumococcus type 20 was cultured. Emergency pericardiotomy was performed at once and 800 cc. of pus were evacuated from the pericardium. There was immediate relief of symptoms of cardiac tamponade and considerable improvement in her general condition. Two days later the right chest was aspirated anteriorly close to the sternum in the hope of finding an empyema which was assumed to be the cause of the pericardial infection. Foul pus was aspirated. The patient was taken to the operating room and a counter-drainage for suppurative pericarditis was performed in this area. No empyema was found, but a small collection of foul pus was evacuated from the lung. It was assumed that this was the source of the pericardial infection. From that time on the course was satisfactory for a period of several weeks. The pericardial wound cleaned up satisfactorily under irrigations. The patient appeared to be making adequate progress. However, nocturnal dyspnea, which was a prominent feature of the clinical course, persisted. This was assumed to be due to a toxic myocarditis, but failed to respond to various types of medical therapy. After a period of three weeks the patient's general condition began to deteriorate, and at one of the dressings a large quantity of foul pus gushed into the pericardial sac from some undetermined source adjacent to the pericardium and obviously on the right side of the wound. It was then assumed that an empyema had probably escaped detection and had perforated into the pericardial sac, but subsequent revision of the pericardiotomy by an approach through the right side of the thoracotomy wound failed to disclose a tract entering the pericardium. The patient's course thereafter was progressively downhill and she eventually died five weeks after the original pericardial drainage.

Necropsy Findings. Between the *heart* and the right *lung* there was a very firm tumor adherent to and invading the pericardium as well as the *diaphragm.* It almost completely compressed the right lung. On section the neoplasm was peculiar in that in some areas it was very cellular, and in other portions there were scattered fat, cartilage, calcification, skin and hair. Microscopically, there were nests of squamous cell carcinoma arising from the epithelial structures of the teratoma. The pericardium contained no free pus. The pericardial sac was, to a great extent, obliterated by fibrinopurulent adhesions.

Comment. Dr. Klemperer. The variety of tissue and cell structure classify this tumor as a teratoma. It obviously had become malignant as evidenced by its invasive tendency grossly, and microscopically the pres-

ence of carcinoma cells. Just as dermoid cysts of the ovary may become malignant, so may similar tumors in other locations undergo neoplastic change as was present here.

Dr. Neuhof. It is of interest and practical import to note that the pericarditis had largely cleared and that death was not due to the pericarditis. The reason is that adequate drainage of the purulent process had been instituted. The case illustrates that the management of suppurative pericarditis should be surgical. Because of the simplicity of the procedure, exploratory aspiration should be performed on a suspicion of the diagnosis, rather than await a full blown picture. The demonstration of pus is an indication for operative intervention.

Reported by *Abner Kurtin, M.D.*

Wednesday, October 18, 1939

Reflex Colonic Obstruction due to Prostatic Hypertrophy with Acute Urinary Obstruction

(From the Medical Service of Dr. Ralph Colp)

History (Adm. 439833; P.M. 11162). This was the first admission of a seventy-one year old male, who for several years had had increased frequency of urination and occasional dribbling after urination. For thirty years he had had a chronic cough, productive of a small amount of sputum which was not foul-smelling. During the previous seven years before admission, he had diabetes, which was controlled by diet. Three weeks before admission, his abdomen began to enlarge, and after two weeks, he developed rather severe abdominal cramps, for which daily enemata were given. During the forty-eight hours prior to admission, the abdominal distention increased and enemata were ineffectual. Except for more or less chronic constipation, he denied any previous gastro-intestinal symptoms.

Examination. The patient was a senile, undernourished man with evidence of recent loss of weight. The arteries of the fundus showed arteriosclerotic changes. There was a small petechial hemorrhage on the lower left eyelid. The chest was emphysematous and there were numerous coarse, moist râles at both lung bases. The heart was apparently normal except for many extrasystoles. The blood pressure was 118 systolic and 70 diastolic. The peripheral arteries seemed thickened. The abdomen was markedly distended and tympanitic, except suprapubically, where the outline of a distended bladder could be palpated. Increased peristaltic sounds were audible. The inferior margin of the liver extended two finger-breadths below the costal margin. The prostate was markedly enlarged, firm, and slightly irregular.

Laboratory data. The urine had a specific gravity of 1.015, and contained a trace of albumin and an occasional white blood cell. The blood urea nitrogen was 29 mg. per 100 cc.; sugar, 155 mg. per 100 cc.; and chlorides, 560 mg. per 100 cc. The blood Wassermann test gave a 4 plus reaction. A barium enema showed an obstruction to the passage of barium in the region of the sigmoid with dilatation of the colon above this area.

Course. Diagnosis was subacute intestinal obstruction, probably due to a low colonic neoplasm. Inasmuch as there seemed to be roentgenologic evidence of an obstructing lesion, a tube cecostomy was performed under local anesthesia on the day following admission, in order to relieve the obstruction. Postoperatively, the temperature rose from normal to 103.2°F. and then descended to subnormal levels. The cecostomy drained very little, and two days postoperatively, oxgall, given through the cecostomy tube, produced a copious bowel movement. The patient was in more or less continuous pulmonary edema and died six days after admission.

Necropsy findings. The *prostate* showed hypertrophy of both lateral lobes, involving the median lobe to a lesser extent. The bladder wall was hypertrophied, showing the usual trabeculations occurring with prostatic obstruction. There was a severe cystitis, which, in places, was necrotizing, and the thickness of the mucosa indicated the chronicity of the cystitis. The *sigmoid* had an area of striking dilatation with thinning of its wall, merging at each end with bowel of usual thickness. There was no evidence of organic obstruction. The transverse *colon* showed a similar area of dilatation. The *small intestine* was collapsed at the time of the autopsy. The *heart* showed some scattered fibrotic scars. The immediate cause of death was an extensive, severe, confluent bronchopneumonia in both lungs which were emphysematous. As an accidental finding, the *liver* had deep depressions on its surface, a picture typical of the syphilitic "hepar lobatum." There were large necrotic nodes of rubbery consistency in both lobes, syphilitic gummas. In the central portion of the liver were many small gummous areas and extensive fibrosis. Some hepatic veins were narrowed by the presence of gummosities.

Comment. Dr. Klemperer: Anatomically, there was no explanation for the intestinal obstruction. In a syphilitic, one thinks of tabes, but in this patient the spinal cord showed no tabes. A few cases of obliterating endophlebitis of the hepatic veins have been ascribed to gumma. Fibrotic scars in the myocardium occur very frequently at that age.

Dr. Baehr: The clinical interpretation was intestinal obstruction due to carcinoma of the sigmoid. This was apparently supported by the x-ray examination of the colon, and by the three-week history of partial intestinal obstruction. The disturbance in bladder function was ascribed quite properly to a secondary effect of the intestinal obstruction upon a man who had suffered from prostatism for a long time. The blood urea nitrogen was only slightly elevated.

Dr. Colp: This case presents several points of clinical interest. On admission, we knew of the prostatic element. In lesions of the kidney, in retroperitoneal hematoma, and with injuries of the retroperitoneal region, intestinal obstruction does occur, but we have never seen such lesions following prostatic disease. Because of the clinical findings and the x-ray visualization of obstruction in the region of the sigmoid, a cecostomy was performed. The patient had a bowel movement on the second postoperative day, following administration of the oxgall. However, no reason for the obstruction could be found. We have had three such cases, all in old men, at the ages of 72, 73, and 79 admitted with intestinal obstruction, in whom enemata became ineffectual. Two of these had lesions at the splenic flexure. I was sure that one had a lesion,

although the X-ray examination showed no lesion near the sigmoid, but found nothing on exploration. Although the cecostomy may give relief, a subsequent X-ray examination should be performed to explain the reason for the obstruction. It can not be taken for granted that there is a lesion.

Dr. Baehr: Dr. Hyman has seen reflex ileus from an overdistended bladder. In this case, the diagnosis of reflex ileus is not proved. At autopsy, the small bowel was collapsed, which speaks against the possibility of reflex ileus or any true intestinal obstruction. There is reason to believe that bronchopneumonia had been present longer than a few days and may have given rise to bowel and bladder disturbances. This old patient had been constipated for years. His constipation was worse for three weeks before admission and he had no bowel movements during the last week. In spite of the distended colon, I cannot agree with the diagnosis of ileus in any form because the small intestine was not distended.

Dr. Moschcowitz: Was there evidence of any intussusception?

Dr. Klemperer: There was no intussusception. All lobes of the lungs showed involvement which was not recent. Anatomically, an estimate of the duration would be about ten days. It was not chronic enough to have preceded the colon and bladder disturbances.

Acute Pyelonephritis Secondary to Renal Calculus With The Clinical Picture of Cholecystitis

(*From the Surgical Service of Dr. A. Hyman*)

History (Adm. 439767; P.M. 11156). This was the first admission of a fifty-two year old Italian woman who had suddenly experienced right upper quadrant pain five days before. The pain radiated to the back and was associated with chills, fever, and drowsiness. She entered another hospital where a diagnosis of acute cholecystitis was made. She refused operation, and two days before admission here left that institution against advice. She became progressively worse, developed icterus, and became irrational. During the two days before admission she received 60 grains of sulfanilamide daily. Her past history included a hysterectomy and bilateral oophorectomy eight years before.

Examination. The patient was a well-developed woman, appearing acutely ill and very drowsy. The pupils were normal. The selerae were icteric. Clotted blood was seen in the right nostril and pharynx. The tongue was furred and dry. Patches of moist râles were found at both bases. The heart revealed no abnormalities. The blood pressure was 96 systolic and 50 diastolic. The abdomen showed a well-healed midline suprapubic scar. Tenderness and some muscle spasm were present in the right upper quadrant; there was no rebound tenderness. No masses were palpable. An ecchymotic spot, 3 centimeters in diameter, was seen on the skin of the abdomen.

Laboratory data. The hemoglobin was 85 per cent; white blood cells, 8,000 (64 per cent polymorphonuclear leucocytes). Admission urine was alkaline with a specific gravity of 1.022. It contained 1 plus albumin, no sugar, no bile, urobilin of

1 to 16, and microscopically showed 2 to 3 white blood cells per high power field. On the following day, the urine was entirely negative for cells, but showed 3 plus sugar after an intravenous infusion of 5 per cent glucose in saline. Blood urea nitrogen was 96 mg. per 100 cc.; blood sugar, 315 mg.; cholesterol, 190 mg.; cholesterol esters, 25 mg.; icterus index, 10; carbon dioxide, 35 vol. per cent; and chlorides, 5 per cent. The blood Wassermann test was negative.

Course. On admission an acute cholecystitis was suspected. Her temperature rose to 105°F. a few hours after she entered the hospital. A blood culture, taken at this time, was subsequently reported as positive for B. coli, 3 colonies per cubic centimeter. There was a rapid down-hill course associated with drowsiness, fever, toxicity, delirium, progressive abdominal distention, and dehydration, in spite of forced intravenous fluids. The day after admission, numerous petechial hemorrhages and occasional ecchymoses appeared on the back. Intravenous infusion was continued, but the patient never responded. Two days after admission the temperature rose to 106.2°F. and the patient died. The clinical diagnosis was B. coli bacteremia secondary to acute cholecystitis.

Necropsy findings. There was no acute or chronic cholecystitis. The left *kidney* was normal in size and showed only slight degeneration. The right *kidney* was enlarged and showed pinhead-sized abscesses on its surface. Only acute pyelonephritis was present. There were no depressed areas on the surface of the kidney. The pelvis was granular. The right ureter was somewhat distended above a small stone at its midportion which completely occluded the lumen and was responsible for the ascending infection. The bladder mucosa was pale and was not infected, but showed submucosal petechiae and hemorrhages, such as occur in generalized infections. Other organs were negative except for some fatty degeneration of the *liver.*

Comment. Dr. Klemperer: The complete obstruction in the right ureter and the uninvolved bladder mucosa explain the negative urine findings. The icterus which occurs with generalized bacterial infections, remains unexplained so far. The heart showed no changes, since there was no localization of the bacteremia on the valves.

Dr. Baehr: This was an unusually rapid course of events for a B. coli bacteremia. The entire clinical course lasted only seven days. The wrong clinical diagnosis of gall-bladder rather than renal disease was based on good reasoning, since all the symptoms favored this diagnosis. There was a slightly increased icteric index and a slight beginning acidosis. The urine failed to reveal any evidences of infection on the day after admission. The blood urea nitrogen of 96 mg. per 100 cc. was higher than is usual for sepsis and should have indicated the possibility of urinary insufficiency. The manifestation of acute bacteremia right at the onset of an acute infection within the abdomen was the only thing to arouse suspicion, since this is unusual with acute cholecystitis but is not uncommon with urinary tract infections. Its acuteness resembled a urethral or ureteral chill following movement of a calculus, with the characteristic entry of organisms into the blood stream. B. coli is common in the urinary tract. In this case, the first downward movement of the minute calculus to obstruct the ureter resulted in a ureteral chill. The presence of B. coli in the urinary tract at the time resulted in a B. coli bacteremia through this portal of entry.

Dr. Hyman: The patient was too sick for urologic or other examinations, being admitted in a drowsy state alternating with delirium. Infusions were the only possible treatment. I have seen a half dozen cases of such sepsis from calculus without instrumentation. B. coli bacteremias usually appear innocuous, and we have seen fifty or sixty cases here which recovered. Acute pyelonephritis with jaundice occurs in infants and was reported from here a few years ago. Use of sulfanilamide now complicates the diagnosis. One case of renal calculus, fever, and cortical abscesses was treated by decapsulation. Jaundice followed the use of only fifty to sixty grains of sulfanilamide, but the patient recovered.

Reported by *Max Ellenberg, M.D.*

CLINICAL NEUROPATHOLOGICAL CONFERENCE

Monday, October 9, 1939

JOSEPH H. GLOBUS, M.D., *presiding*

Case 3.[1] Pinealoma

(From the Neurological Service of Dr. I. S. Wechsler)

History (Adm. 435254; P.M. 11068). A man, 62 years of age, had a bilateral mastoid infection in infancy. He had been deaf since then and, because of his deafness, he had not learned to speak clearly. For two years prior to his first admission to the hospital (October 12, 1938) he had been subject to periodic attacks which would begin with a feeling of "hot blood rushing to his head." He would break out in a profuse sweat and his right arm would shake. Shortly thereafter, he would become dizzy, would tend to fall to the right side, and on several occasions did fall but without losing consciousness. These attacks would recur once or twice daily, each lasting for ten to fifteen minutes. With these attacks he occasionally experienced fronto-occipital headache. In the course of time, beginning with June 1938, the attacks became more frequent and of longer duration. During the next few months he began to display lapses of memory; dizziness became almost constant. At times he was confused and disoriented. His vision became impaired. He experienced prickling and a dull aching sensation in his legs. He would drag his legs, particularly the right one, and would stagger when walking. He became increasingly drowsy and apathetic.

Examination. The patient was dysarthric. He walked on a broad base, dragging his legs and balancing himself with outstretched arms. The Romberg test was markedly positive. His pupils were small and unequal, the right being slightly larger than the left. They did not react to light but would dilate slowly in the dark. They reacted poorly, if at all, in accommodation but better when dilated with cocaine. The nasal portions of both discs were slightly blurred. The retinal vessels showed slight arterial-venous notching. Colloid excrescences of the lamina vitrea (*drusen* formations) were present. There was almost complete paralysis of upward gaze. On lateral gaze there were nystagmoid movements, more definite to the right. Perimetry disclosed some constriction of vision in the lower nasal quadrant on the left; but this may have resulted from the patient's failure to understand orders during the test. There was a bilateral complete nerve deafness. A slight tremor and some dysdiadochokinesis were present in the left upper limb. The lower limbs were somewhat weak. The deep tendon reflexes were equal and active. The Babin-

[1] The first two cases were reported in the preceding issue of the Journal (Vol. 7, No. 1).

ski sign was present on both sides. There was a suggestion of a positive Kernig sign bilaterally. The abdominal reflexes were barely obtained and readily exhausted. Heel-to-knee tests were poorly performed bilaterally. Vibration sense was diminished in the toes, while position sense seemed to be diminished in the smaller toes. The blood pressure was 150 systolic and 92 diastolic.

Laboratory data. The blood, urine, and cerebrospinal fluid examinations, including Wassermann tests, were all negative. A gastric analysis was likewise negative. Caloric tests gave normal responses. An electrocardiogram was reported as showing left ventricular preponderance, suggestive of hypertrophy of the left ventricle.

Course. Among the diagnoses considered were central nervous system syphilis, subacute combined degeneration, midbrain tumor, and cerebral arteriosclerosis. During the patient's stay in the hospital, an impairment of left lateral gaze appeared. In spite of a provocative injection of neoarsphenamine, the Wassermann reactions continued to be negative. An encephalography was performed which showed a dilated fourth ventricle. The anterior border of the fourth ventricle appeared somewhat depressed. No air was seen in the ventricular system anterior to this level, only a moderate amount of air was seen outlining sulci and the basilar cisternae, while a considerable amount of air was seen about the cerebellum. The appearance was reported as suggesting a midbrain lesion. Sixteen days after admission (October 28, 1938), the patient requested that he be discharged, stating that he was feeling better. His ataxia did seem to be somewhat less marked.

Interval history. During his stay at home he was bedridden and his condition declined rapidly. He would occasionally try to get out of bed but would bruise himself in these attempts. His intellect continued to disintegrate; his memory and judgment depreciated. At one time he wanted to put on his dress suit so as to go out for a morning walk; at another time he refused to eat, for he said the food had come from Germany; and again, he requested that his wife be called home, although she was in the room at the time. He frequently complained that the lights were too bright. He became voracious and vomited on several occasions. Headaches of short duration at the vertex and right frontal regions would occur at two to three day intervals. Two weeks before admission the patient became incontinent of urine and, for the last few days, had had to be fed, as he could no longer find his mouth.

Second admission (January 23, 1939). The patient seemed disinterested in his surroundings but apparently remembered and recognized the examiner. His gait could not be tested. He cooperated poorly. His pupils were small and irregular and did not react to light or in accommodation. They dilated fairly well with homatropine. Upward gaze was limited and neither eye reached the external canthus on lateral gaze. On left lateral gaze there were a few inconstant nystagmoid jerks. There was a slight ptosis of both lids. He was totally deaf. Mild photophobia was present. The nasal portions of the discs were somewhat blurred. The visual fields could not be tested. On finger-to-nose testing the patient pass-pointed with both hands. Skilled acts were fairly well-performed. There was a slight tremor of the extended fingers, left more than right. The deep and superficial reflexes were equal and active. The Babinski and Chaddock signs were present on both sides.

Laboratory data. Blood and urine examinations were negative. The cerebrospinal fluid was clear and under an initial pressure of 210 mm. of water. The final pressure was 100 mm. of water. The Ayala index was 4.8. The fluid contained many well-preserved red blood cells and 25 mononuclear cells per cubic millimeter; Pandy, 3 plus; total protein, 51 mg. per cent; chlorides, 720 mg. per cent as NaCl; the colloidal gold and Wassermann tests were negative.

Course. During his stay in the hospital the patient developed paresis of the right lower extremity, depression of all deep reflexes, and what appeared to be a glove and

stocking hypalgesia. He became drowsy and lethargic, almost unresponsive. A ventriculography was then performed. This was reported as revealing a huge dilatation of both lateral ventricles, symmetrical about the midline. Posteriorly there seemed to be a slight displacement of the interventricular septum to the left. The third ventricle was also symmetrically dilated in the midline. That part of the aqueduct which was visualized appeared dilated and the upper end of the fourth ventricle was thought to be filled. These findings suggested the presence of an obstructive lesion in the aqueduct or the superior portion of the fourth ventricle. In addition there was also a slight decalcification of the floor of the sella turcica and of the dorsum sellae and the pineal gland appeared to be displaced posteriorly. Following ventriculography the patient's temperature rose to 102°F. On the following days he seemed to be more alert and more aware of his environment. On the fourth day after the ventriculography there appeared a sudden change; he vomited and became drowsy, vomited again and became stuporous. This was followed by a convulsion lasting about five minutes and involving the right shoulder and arm. He was given 250 cc. of 50 per cent sucrose intravenously. At this time his pupils were fixed to light and unequal, the right pupil being contracted, while the left was dilated. All extremities were flaccid and a bilateral Babinski sign was obtained. A ventricular tap was done and 45 cc. of clear fluid was removed. Respirations improved but the patient remained in coma. In the early evening it was observed that the left pupil was still larger than the right one. The patient died a few hours later.

Necropsy findings. Gross. The leptomeninges were dull. The superficial meningeal blood vessels were engorged. In the right frontoparietal region there was a small, round area of reddish discoloration, the site of the ventriculography. The left cerebral hemisphere was larger than the right. All of the cerebral convolutions were broadened and the sulci were almost obliterated, more so on the left side. The brain felt softer than normal. The optic nerves, chiasm, and tracts were flattened and the optic nerves and tracts were further apart at the chiasm than normal. There was slight arteriosclerosis and thickening of the left vertebral artery.

On sectioning of the brain, there was found an enormous internal hydrocephalus, affecting both lateral ventricles, the third ventricle, and the aqueduct of Sylvius (fig. 7A). A small portion of tumor tissue was found to be attached to the left lateral wall of the aqueduct at the point where the mesencephalon seemed to be fused with the pulvinar. Tracing the aqueduct posteriorly, it was found to be markedly enlarged and completely blocked by tumor tissue. The tumor tissue had completely replaced the quadrigeminal plate and the dorsal part of the tegmentum. At this point the tumor measured about $2\frac{1}{2}$ cm. in the vertical plane and about 2 cm. in the horizontal plane. Directly above this tumor, and fusing with it, was the pineal body. It was still attached to the dura dorsally. In the left part of the tumor, occupying its ventrolateral area, there was a small cyst filled with grayish-yellow gelatinous material. Ventral to the tumor, the midbrain and pons displayed numerous congested blood vessels with petechial hemorrhages. The tumor apparently extended as far back as the transition of the aqueduct into the fourth ventricle. The upper part of the fourth ventricle showed some discoloration in its floor, due to the close proximity of the tumor. The fourth ventricle was large and was almost completely occupied by a displaced vermis covered by choroid plexus.

Microscopic. Serial cross sections of the midbrain and the attached pineal body, stained with hematoxylin-eosin, disclosed two areas of tumor tissue, one in the pineal gland, the other in the midbrain (fig. 7B). The aqueduct was found to be completely displaced to one side and a tumor mass occupied the ventral part of the tectum and the dorsal part of the tegmentum. In one series of sections, tumor tissue in the pineal was continuous, on the right side, with tumor tissue in the midbrain.

The tumor tissue was very cellular and vascular. It was well-demarcated from

the surrounding brain tissue, which was compressed. Most of the cells were poorly differentiated and contained large nuclei, rich in chromatin. The cytoplasm was scanty. The cells were usually arranged in large compact groups. In some areas they tended to form rosette-like or alveolar structures (fig. 7C), such as are seen in the pineal body during the twentieth to twenty-fourth months of life. Around many blood vessels the cells often assumed a form resembling ependymal cells. Here their nuclei were located at the pole of the cell away from the vessel. Some such cells

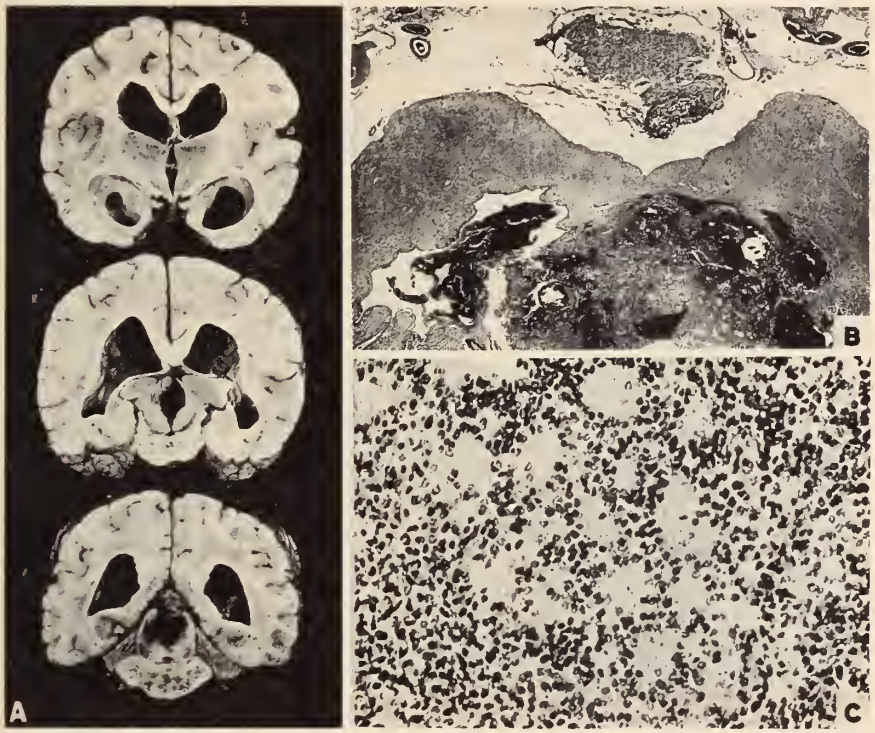

FIG. 7 (Case 3). A. Coronal sections of the brain showing the tumor in the tectum and tegmentum of the midbrain obliterating the aqueduct of Sylvius and extending into the wall of the diencephalon on the left side. The pineal body is large and on its ventral aspect is in contact with the tumor mass in the midbrain. There is an enormous internal hydrocephalus affecting the lateral and third ventricles.

B. A section of the midbrain and pineal body at a level caudal to the site of their contact showing a small area of tumor tissue in the pineal and the extensive midbrain tumor, richly vascular with extensive extravasation of blood (Hematoxylin-eosin, 350 ×).

C. An area of tumor tissue showing the tendency of the tumor cells to form pseudo-alveolar arrangements (Hematoxylin-eosin, 10 ×).

showed vacuoles in the pole toward the perivascular space. Strands of pink-staining substance were occasionally found in some of the perivascular spaces bordered by these cells. No mucin, however, was disclosed with Mayer's muci-carmine stain. These perivascular ependyma-like formations resembled structures found in the pineal bud before the sixth month of fetal life.

In the pineal body the tumor occupied the ventral third of the gland. Within this portion of the tumor there were two well-defined, oval areas characterized by

many clear-cut fusiform spaces of varying size (fig. 8A) associated with multinucleated, foreign body giant cells. These spaces are typical of the cholesterin crystal formations occurring in embryonic rests. The remainder of the pineal gland was normal for the patient's age and showed also an ependymal-lined space, the closed off remnant of the primitive pineal diverticulum. In appearance this resembles the ependyma-lined prolongations from the aqueduct of Sylvius normally found projecting finger-like for short distances into the midgrain. In this case such prolongations into the midbrain were more or less obliterated by the tumor growth. However, a short distance away from the mass of the tumor, the ependyma of such invaginations was intact but was accompanied by a subependymal band of loosely arranged tumor cells (fig. 8B).

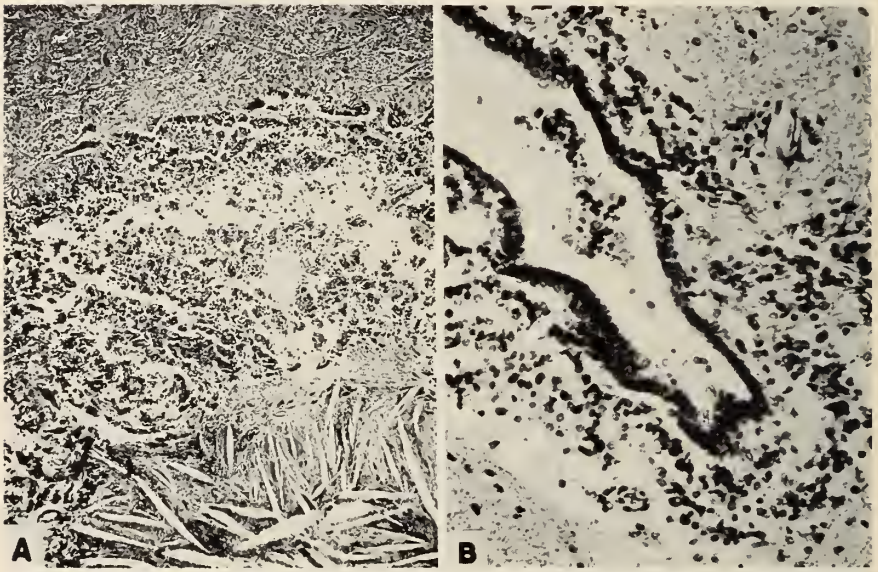

FIG. 8 (Case 3). A. A section of the pineal body showing three distinct zones: pineal tissue, tumor tissue, and an area of cholesterin crystal deposits (Hematoxylin-eosin, 52 ×).

B. An ependymal-lined diverticulum in the peri-aqueductal region surrounded by a subependymal zone of tumor cells (Hematoxylin-eosin, 290 ×).

The blood vessels within the tumor showed thickened and distorted walls. The perivascular spaces were usually enlarged. Quite extensive extravasations of intact red blood cells were spread through the tumor, as well as deposits of yellowish-brown pigment representing previous extravasations of blood.

Comment (*Dr. Globus*): The occurrence of a pineal tumor in an adult at the age of 62 years is quite unusual, for this type of tumor, because of its teratoid character is a lesion most commonly found in the adolescent. Otherwise the clinical diagnosis should not offer any difficulties. The paralysis of upward gaze, the Argyll-Robertson pupils (though somewhat atypical) in addition to other manifestations of brain stem involvement, in the presence of progressing papilledema pointed definitely to an expand-

ing lesion in or about the quadrigeminal plate and since the most likely lesion there is of pineal origin, hence pinealoma was the most likely diagnosis.

Histologically the tumor shows some departure from the typical pinealoma by lacking the mosaic character of cell organization, such as is seen in the pineal body during its first month of postnatal development. On the other hand it reveals other histological patterns duplicating other histogenetic stages in the developing normal pineal. In addition, it contains many spongioblastic elements, probably ependymal in origin, attesting to its malignant character.

Reported by *J. M. Zucker, M.D.*

Case 4. Schwannoma; Right Ponto-Facial Angle

(From the Neurological Service of Dr. I. S. Wechsler and the Neurosurgical Service of Dr. I. Cohen)

History (Adm. 435394; P.M. 11066). A man, aged 57 years, had experienced gradual failing of hearing in the right ear for ten to fifteen years. Two years before admission to the hospital he became subject to frequent frontal headaches which would last several days at a time and were occasionally associated with vomiting. Soon afterward he began to complain of vertigo which increased in severity so that six months later (July 1937) he was forced to discontinue work. Meanwhile his deafness had rapidly become more marked. At the same time, difficulty in walking set in with a tendency to stagger to the right. He entered a hospital on July 28, 1938 where the diagnosis of right cerebellopontine angle tumor was made. Operation was advised but was refused by the patient. Shortly thereafter his vision began to fail and about six months later he became unable to walk unless assisted. He then entered the Mount Sinai Hospital (January 26, 1939).

Examination. The patient was obese. He was slow of thought. His speech was somewhat incoherent and rambling. He displayed a marked tendency to facetiousness and at times would explode into unprovoked laughter. He could walk only with support and would shuffle along on a broad base with his eyes fixed on the floor. Whether walking or sitting, he would tend to fall to the right. His pupils were dilated; the right one was slightly irregular. They reacted sluggishly to light and in accommodation. Bilateral papilledema of 3 diopters with small retinal hemorrhages was present. His visual acuity was O. D. 20/200 and O. S. less than 20/200. There was limitation of upward and lateral gaze. Nystagmus with a rotary component was present. The right masseterie group of muscles seemed weaker than the left. The right corneal reflex was absent. There was a right supranuclear facial paresis. The hearing and calorie tests indicated a total loss of function of the right cochlear and right vestibular nerves. The deep tendon reflexes of the right lower extremity were greater than those on the left side. An Oppenheim sign was obtained on the right side. The upper abdominal reflexes were feeble and readily exhaustible. The lower abdominal reflexes were absent. The cremasteric reflexes

were active and equal. The extremities showed marked dyssynergia, especially on the right side.

The patient was dyspneic and his respirations were whcezing. His heart was slightly enlarged, and its sounds were of poor quality. The blood pressure was 124 systolic and 72 diastolic. Occasional sibilant râles were heard at the base of the lungs. Small papillomatous growths were noted in the axillae and one such growth was present over the left occiput.

Laboratory data. Red blood cells, 4,340,000 per cu. mm.; hemoglobin, 88 per cent; white blood cells, 6,200 per cu. mm.; differential, 72 per cent, polymorphonuclear leucocytes. The blood chemistry was normal. Urine, one plus albumin. An electrocardiogram showed a left ventricular preponderance. The cerebrospinal fluid was under an initial pressure of 240 mm. of water. The final pressure, after 5 cc. were removed, was 180 mm. of water. Ayala index, 3.75. The examination of the fluid showed 4 monocytes per cu. mm.; Pandy, 4 plus; total protein, 93 mg. per cent; colloidal gold, 1111100000. Blood and spinal fluid serologic tests were negative. An X-ray examination of the skull was reported as showing distinct destruction of the right petrous apex about the *porus acusticus internus*, a change which was considered very suggestive of an *acoustic neurinoma*. On the left side of the vertex, an area of rarefaction extended through both inner and outer tables and had sharply defined borders. It was believed to represent a cystic area, or, less probably, a unilateral enlargement of the parietal foramen.

Course. The diagnosis of a right cerebello-pontine angle tumor, probably an acoustic neurinoma, was made. Five days after admission, a suboccipital craniotomy was attempted. While the local anesthesia was being administered, the patient sank into deep stupor. To relieve this condition a right ventricular puncture was done. Clear fluid escaped under greatly increased pressure, indicating the presence of an internal hydrocephalus. The patient did not regain consciousness and the craniotomy was continued. An encapsulated tumor was found in the right cerebello-pontine angle and an intracapsular removal was performed. The patient remained unconscious and died within twenty-four hours.

Necropsy findings. Gross. The calvarium, at about the apex of its vault, presented two extensive areas of bone erosion on its inner surface. Furthermore, the left petrous bone was eroded in the region of the internal auditory meatus over an area about 1½ centimeters in diameter. The leptomeninges appeared normal except for engorged blood vessels. The cerebral gyri were flattened and the sulci were narrowed. Both temporal poles were adherent to the dura. The normal markings of the right cerebellar lobe especially on its antero-lateral aspect dorsally and ventrally, were obliterated by the presence of an irregular, soft, gelatinous reddish-yellow mass of tissue (fig. 18). The left cerebellar hemisphere was bound to the dura in places. The cerebral hemispheres were of normal consistency. The stalk of the hypophysis was greatly thickened. The floor of the sella turcica was represented by only a layer of fibrous tissue.

On sectioning the brain, a remnant of tumor tissue was found in the right ponto-facial angle. Its size was estimated to be about one-fifth of the original tumor mass. The pons was displaced by the tumor to the left and showed marked disorganization and discoloration. The lateral ventricles were symmetrically and markedly dilated. The aqueduct was narrowed and displaced upward and to the left. The fourth ventricle was deformed and also displaced to the left.

Microscopic. A section of the tumor, stained with hematoxylin-eosin, disclosed tumor cells arranged in streams and whorls. The cells were fusiform in outline and their nuclei, which were similarly elongated, often appeared in the characteristic palisade arrangement (fig. 10).

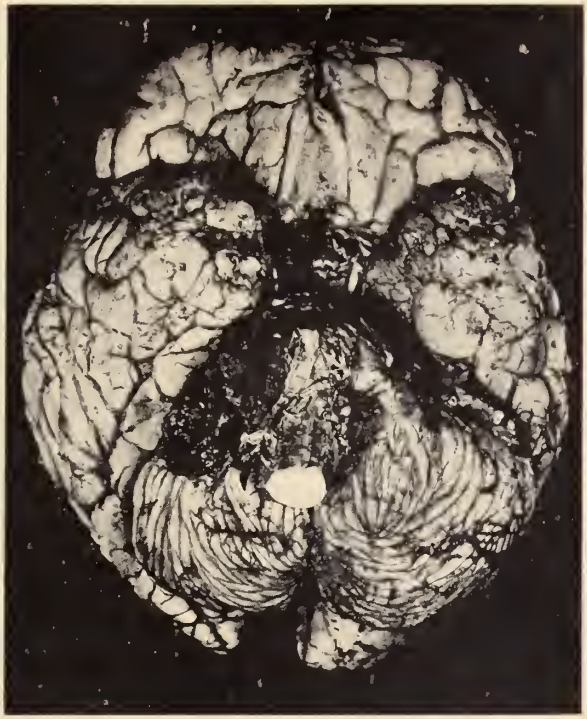

FIG. 9 (Case 4). The site of the tumor is marked by the discolored mass in the right cerebello-pontine angle.

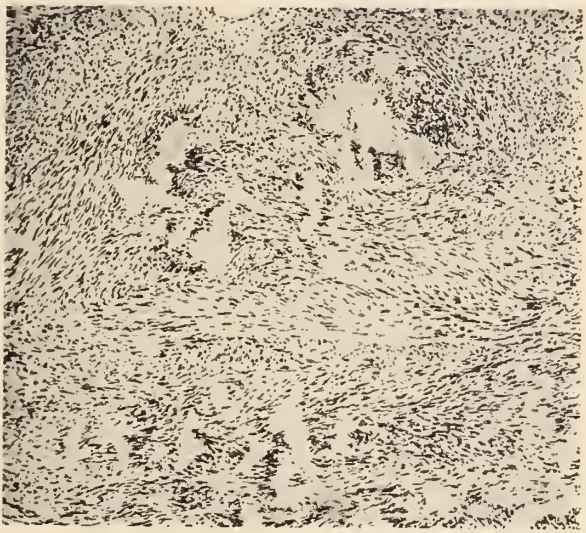

FIG. 10 (Case 4). A section of tumor tissue showing palisade, whorl, and stream formations (Hematoxylin-eosin, 90 ×).

The blood vessels were fairly abundant and many were thickened. Accumulations of cells containing yellowish brown pigment were found about some of the vessels. Extravasation of red blood cells and areas of necrosis were also present.

The van Gieson stain disclosed only a slight amount of collagenous fibers in the tumor tissue.

Comment (Dr. Globus): The history in this case is quite typical for this form of pontofacial angle tumor, usually termed acoustic neuroma. It may be said that in this instance the tumor can be traced to the time the patient first noticed impairment of hearing on the affected side. Deafness is probably the earliest symptom of a brain tumor of this type and in this location. It is a symptom often not fully appreciated and not properly evaluated. But when it is established to be of the nerve deafness variety it should draw attention to the probability of the existence of an acoustic tumor. Caloric tests, if confirmatory, will clinch the diagnosis and lead to surgical intervention at an earlier and hence, more favorable time.

Of course, when papilledema, cerebellar manifestations, and other signs of increased intracranial tension appear, then the diagnosis is less difficult, but the favorable time for operation may have passed.

Reported by *Jacob H. Friedman, M.D.*

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.

Heminephrectomy in Disease of the Double Kidney. Edwin Beer and W. H. Mencher. Ann. Surg. 108: 705, October 1938.

A series of 104 cases of double kidney is presented and an analysis of these cases emphasizes the well known statement that an anomalous kidney is prone to disease. Sixty per cent of these cases had symptoms, and 25 per cent required some operative procedure. Fourteen of these cases required a heminephrectomy in which there was a single operative mortality, or 7 per cent. The disease was limited to the upper pole in four cases (28 per cent), and of these four cases, two had ectopic ureters. The upper pole and its ureter were removed, preserving for the patient the lower half of the kidney. In ten cases, the lower pole showed involvement, and in these the lower half was removed, allowing the upper portion to remain. The nature of the lesion in six cases was pyonephrosis; in five cases it was hydronephrosis: one case had a calculus hydronephrosis; in two cases there were multiple calculi. In none of the cases was it necessary to perform a secondary nephrectomy of the residual portion. In those cases in which there was a follow-up by cystoscopy or pyelography, all of them showed good function of the remaining portion of kidney at variable lengths of time after the operation. The conclusion is reached, that conservation of renal tissue is indicated in instances of double kidney, and that heminephrectomy fulfils this purpose.

The Effect of Radiation Applied Directly to the Brain and Spinal Cord. L. M. Davidoff, C. G. Dyke, C. A. Elsberg and I. M. Tarlov. Radiology 31: 451, October 1938.

The effects of radiation directly through the open wound were studied on a series of macaeus rhesus monkeys, and the clinical effects and pathological lesions found at autopsy reported upon. The interesting finding was that the blood vessels of the brain are relatively little affected by the direct radiation.

The Influence of Experimental Biliary Obstruction and Liver Injury upon the Total Bile Acid Content and Partition in Blood and Urine. S. S. Lichtman. Am. J. Physiol. 124: 94, October 1938.

A technic for the estimation of the total bile acids and partition into cholic and "non-cholic" acid fractions, has been devised for the blood and urine. The procedure relies on the author's hemolytic method for the estimation of total bile acids and the Josephson colorimetric method for the estimation of cholic acid in the blood. The author adapted the Josephson procedure for use in urine analysis for cholic acid.

The effect of experimental biliary obstruction and liver injury induced by carbon

tetrachloride upon the total bile acid content and partition in the blood and urine was tested. Acute liver injury induced by a single dose of carbon tetrachloride was found to decrease the total bile acid content of the blood and generally the cholic acid fraction. The total bile acid concentration in the urine was usually found to be increased simultaneously. Complete biliary obstruction, on the other hand, produced a marked increase in the total bile acid content and cholic acid fraction in the blood. Bile acid and cholic acid concentration in the urine were also found to rise markedly.

Radical Treatment of Intractable Pruritus Ani. S. D. Manheim and L. J. Druckerman. Surg. Gynec. & Obst. 67: 500, October 1938.

The authors report three cases of severe and intractable pruritus ani accompanied by advanced cutaneous changes. They did a complete excision of the entire perianal skin up to, and including, the muco-cutaneous margin. The sphincter muscles are carefully exposed and protected and the mucosa of the anal canal is mobilized and sutured to the free borders of the gluteal skin, which is also mobilized. The results were gratifying. Pruritus disappeared completely. Complete healing occurred in from six to ten weeks. All three patients had remained well and symptom-free up to twenty-two months after operation. The method is not recommended for the treatment of the usual case of pruritus ani, but only for long-standing, intractable pruritus ani, particularly when accompanied by pronounced and possibly premalignant cutaneous changes.

Partial and Complete Heart Block in Acute Coronary Artery Occlusion. A. M. Master, S. Dack and H. L. Jaffe. Am. J. M. Sc. 196: 513, October 1938.

The authors have made a detailed study of the disturbances in A-V conduction in 375 personally observed cases of acute coronary artery occlusion. Simple P-R prolongation occurred in 16 per cent of the cases, and partial and complete heart block in 3.2 per cent. The onset of any of these may be the first or only sign of coronary occlusion. There were several important differences between simple prolongation and complete or partial block; the latter usually appeared soon after the attack and lasted one to two weeks, whereas the former not infrequently appeared late and became permanent. Complete heart block was associated with heart failure and cardiac enlargement, and with a heart rate usually 40 or less; as a result, the prognosis was poor. P-R prolongation was innocuous, as was partial heart block, unless the rate fell to 40. Complete and partial heart block were associated with characteristic electrocardiographic and pathological changes, namely, infarction of the posterior portion of the interventricular septum and left ventricle (occlusion of right coronary artery) and the Q-3 T-3 pattern in the electrocardiogram. In P-R prolongation there were no specific changes in the electrocardiogram or at necropsy. Special therapy is of value only when Stokes-Adams seizures occur; adrenalin should be used.

Sulfanilamide Therapy for Suppurative Pylephlebitis and Liver Abscesses. R. Ottenberg and M. Berck. J. A. M. A. 3: 1374, October 8, 1938.

The report is concerned with the successful results of sulfanilamide therapy in two cases of suppurative pylephlebitis. The effectual use of the drug for B. coli infections prompted its application in this disease. One of the cases is of particular significance in that a biopsy of the liver, secured at secondary laparotomy, definitely proved the presence of the lesion of suppurative pylephlebitis with peri-phlebitic abscess formation within the liver. This proved case of post-appendicial suppurative pylephlebitis with multiple liver abscesses recovered completely following the use of the drug. A microphotograph of the hepatic lesion is presented.

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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.

Changes of address must be received at least two weeks prior to the date of issue, and should be addressed to the Journal of The Mount Sinai Hospital, Mt. Royal and Guilford Avenues, Baltimore, Maryland, or 1 East 100th Street, New York City.

TO

DR. HOWARD LILIENTHAL

PIONEER AND LEADER IN HIS CHOSEN FIELD,

THIS VOLUME IS DEDICATED

ON THE OCCASION OF HIS EIGHTIETH BIRTHDAY

AS A TOKEN OF ESTEEM AND AS AN

EXPRESSION OF APPRECIATION, AFFECTION

AND GOOD WISHES

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THE ANNIVERSARY VOLUME COMMITTEE

WISHES TO EXPRESS ITS APPRECIATION

TO THE MOUNT SINAI HOSPITAL

FOR MAKING POSSIBLE THE DEDICATION OF THIS

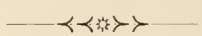
SPECIAL ISSUE OF THE JOURNAL

TO DR. HOWARD LILIENTHAL,

A BELOVED AND ESTEEMED COLLEAGUE, WHO

HAS GIVEN FIFTY-FOUR YEARS OF

DEVOTED SERVICE TO OUR HOSPITAL



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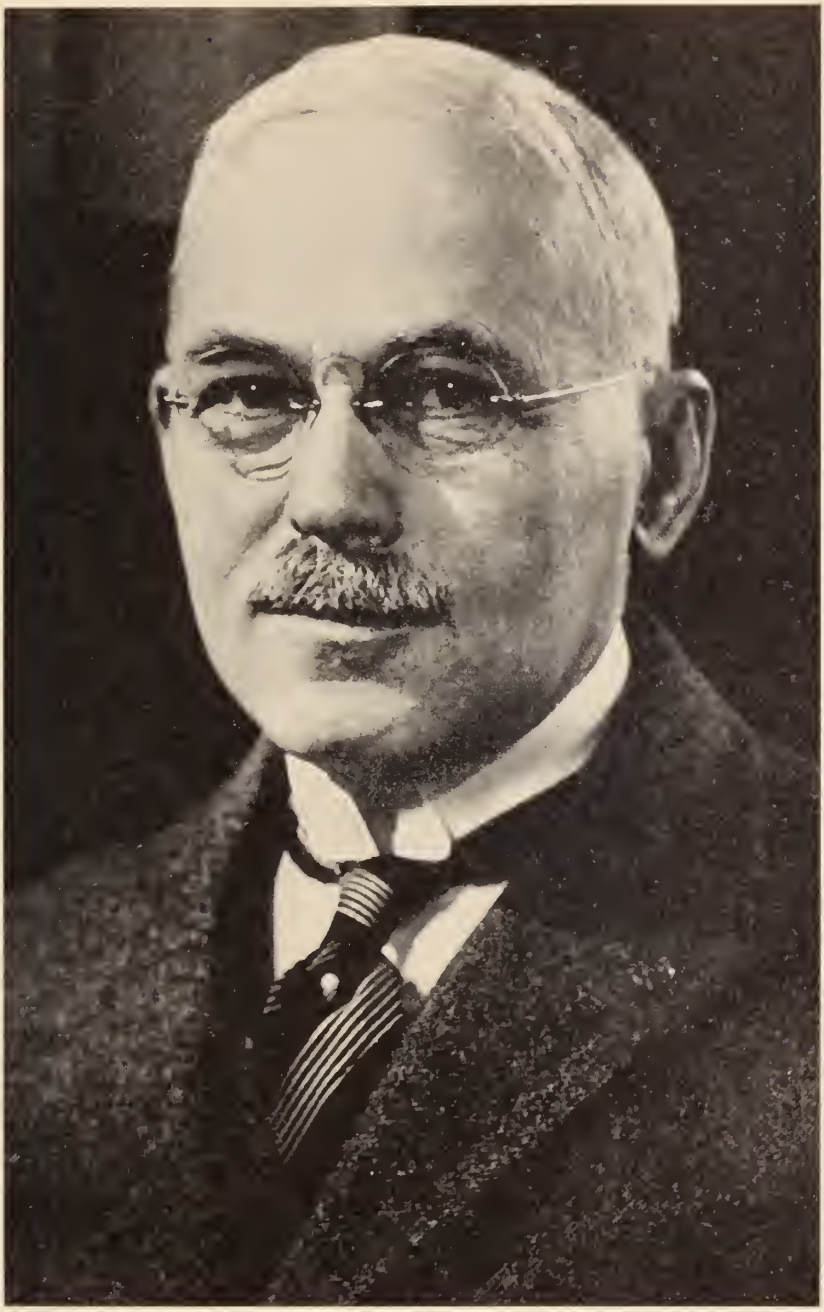

Howard Pillsbury

FOREWORD

It is a privilege to be asked to write a foreword for this volume in honor of Dr. Howard Lilienthal and to pay this brief personal tribute to him. During his long and honorable career he has seen and participated in most of the development of modern surgery. The aseptic surgery developed by von Bergmann as a modification of Listerism had just come over the horizon when Dr. Lilienthal began his career, and visceral surgery which was first developed in the abdomen was in its beginning. He became a master of that field. He was one of the first to urge cholecystectomy as a more common operation than the more usual cholecystostomy. I well remember an expression which he used in a discussion at one of the first meetings of the American Surgical Association which I attended. He stated: "If the gallbladder needs an operation at all it should be removed."

But it was the inviting, almost unexplored field of the thoracic cavity which called forth his most brilliant work. Those of us who have followed his leads owe him a tremendous debt for his inspiration and for the encouragement which he has always generously given to young men who have honestly striven to improve their results and to make original contributions to that field. He has sometimes been sharp in his discussions and impatient with obviously inaccurate and poorly prepared papers presented at meetings, but there has never been any personal rancor. In fact he usually accompanied his sharpest criticisms with helpful suggestions inspired by his extensive experience.

The American Association for Thoracic Surgery, although founded by Willy Meyer, owes much of its present strength and success to Dr. Lilienthal. The devotion with which he used to attend every meeting and the enthusiasm which he displayed were contagious to us cubs. He was one of the great triumvirate who gave the Association a successful start, Willy Meyer, Howard Lilienthal and Rudolph Matas.

Dr. Lilienthal published the first considerable series of cases of lobectomy for bronchiectasis. Although his mortality figures in those early cases would have been discouraging to many, they did not shake his resolute and indomitable pioneering spirit. Moreover his series was a demonstration that it is not merely a chance lucky patient who will survive the operation but that in good risk cases the patients are likely to survive. These operations of his at that time without the benefit of modern diagnostic methods of accurate localization and without many of the modern technical procedures which increase the safety of the operation, and even in the face of hostile criticism from some of his colleagues, are good evi-

dence of his courage, his self-reliance and his independence. These are the qualities which make a pioneer but they are likely to lead one astray, especially in surgery, unless they are tempered with common sense. Dr. Lilienthal is richly endowed with that quality also.

The posterior mediastinotomy for carcinoma of the esophagus was a landmark in that field and his case was one of the first of the successful resections of the thoracic esophagus. His book, "Thoracic Surgery" in two volumes, published nearly twenty years ago, is still a classic because it contains many of the original contributions of Dr. Lilienthal to the field and is a rich harvest of his great experience.

The best evidence, however, that he has been a master surgeon and an inspiring leader is obtained not from his writings but from the devotion of his pupils. In this respect the old adage, "It's hard for a king to be a king to his valet," has a bearing here. This volume of papers contributed by those who have been associated with him at The Mount Sinai Hospital to do him honor on his eightieth birthday is an unmistakable indication that even to those who know him best he has been a master.

Evarts A. Graham.

AN APPRECIATION OF HOWARD LILIENTHAL

MORRIS MANGES, M.D.

Among the pupils and the colleagues of Howard Lilienthal, in this their tribute to him on his eightieth birthday, I also should be included. I have enjoyed an unbroken friendship of fifty years in our professional and social relations. I, too, have been deeply influenced by his accomplishments and his teachings at The Mount Sinai Hospital.

The miracles of the chemists now usurp the full attention of the day and obscure the solid foundations upon which medicine and surgery have been reared. The path of today and that of tomorrow may be easier and less laborious; yet the broad road had been hewed by the labors of the older leaders.

Lilienthal has been outstanding among them. His work has been in many fields, each of which has been made fruitful by his genius. He has been recognized as a master in surgery and he has the originality and the skill which have brought success, the evidences of which are found in many publications. In medicine and mental diseases, he has always been deeply interested.

His contributions to medical literature have been characterized by his unusually fine style of writing.

Lilienthal is also a many sided man, in his avocations as author, soldier,[1] painter, musician, inventor, naturalist and fisherman.

If I am to emphasize some of his characteristics, I would stress the man who is ever young, and who is full of enthusiasm, and who ever has urged his slogan that "you have not been the first and you will not be the last." He has uttered these words as long as I have known him. Only a few days ago, when we discussed a recent discovery, he at once visioned its possibilities.

Alongside of his imagination, I wish to refer to his pioneer work in thoracic surgery, carrying on almost alone in this country. Today these operations are nearly commonplace with thoracic surgery a specialty and its literature growing rapidly. It is hard to believe that only fifteen years ago, in 1925, Lilienthal published his monumental classic, "Thoracic Surgery," the first in this country. It is the results of his experiences and his

[1] Commissioned a lieutenant in the Medical Reserve Corps in 1911 and as a Major in 1917, Dr. Lilienthal went overseas as director of Base Hospital #3. He was promoted to Lt. Colonel in 1918 and served as head of an operating team at the Evacuation Hospital #8 in the Meuse Argonne and St. Mihiel sectors. On May 1, 1921 he was cited for the D. S. M.

studies in every part of the thoracic cavity in this most difficult field, a *terra incognita* for the surgeon.

When in 1911 Elsberg introduced intratracheal anaesthesia, Lilienthal at once had perceived its practical possibilities for the lung to overcome the difficulties of the cumbersome pneumatic chamber. For a long time, these difficulties were very great, the results were meagre, and the mortality was high. Especially was this condition in lobectomy so appalling that only a courageous surgeon ever dared to operate.

He was alone in this field at The Mount Sinai Hospital; none of his surgical colleagues supported him. It was only too often said at the hospital that "Lilienthal had had another lobectomy failure." The physicians shared the same skeptical attitude.

I was alone in my belief in Lilienthal as I had watched his work. I knew the man, I had faith in him and I was willing to trust my patients to him. This judgment has been justified, for his courage, knowledge and skill have made lobectomy and so many of the accomplishments in thoracic surgery possible.

I wish to include another side of Lilienthal, his humane relations with all his patients. Especially were these shown in the care and the solicitude for those afflicted with chronic pulmonary disease, suffering so long, and so poor. He helped many of them with money or obtained small funds from friends. Day or night, he never spared himself in their service and encouraged them in their long fight for cure or relief.

SOME PATHOLOGICAL FEATURES OF PRIMARY AND SECONDARY EXTRAMEDULLARY TUMORS OF THE SPINAL CORD[1]

CHARLES A. ELSBERG, M.D.

It is with especial gratification that I dedicate this short paper to Dr. Howard Lilienthal. The first spinal cord operations performed by me were during the period that I was an adjunct surgeon on the Surgical Service of Dr. Lilienthal at The Mount Sinai Hospital. The many years that have passed since then have steadily increased the esteem and friendship that I have felt and feel for him. It is a sincere pleasure to add my tribute to him in this volume dedicated to him on his eightieth birthday.

1. In a series of primary and secondary tumors of the spinal cord which came under the care of the writer, in all of which the growths were histologically verified at operation, there were 267 cases of extramedullary tumor. These 267 cases form the basis for the observations which are here presented. In view of the existing confusion in terminology, no attempt will be made to enter into a discussion of nomenclature or to explain the reasons for the use of the term perineurial fibroblastoma suggested by Mallory (8) and by Penfield (9) for the growths called neurinoma, schwannoma, neurofibroma, etc., by others, and for the use of the term meningeal fibroblastoma for the histological types of growth that were formerly called endotheliomas, and that now, in order to avoid the issue, are so often called meningiomas.

The relative frequency with which different types of growth were encountered is shown in Table 1.

This table shows that, in our experience, the perineurial and the meningeal fibroblastomas formed 46 per cent of all of the growths and 68 per cent of intradural growths. Of the extradural growths, the most frequent are the primary sarcoma and the herniation of the nucleus pulposus—if the latter can properly be called a neoplasm. As the table is based upon a series of tumors encountered in the operating room, the number of extradural growths is relatively small because the majority of patients with metastatic spinal disease are not operated upon.

[1] Read at the Third International Cancer Congress, Atlantic City, New Jersey, September 14th, 1939.

2. The growths were found at the vertebral levels shown in Table 2.

If the figures in Table 2 are compared with the relative number of cervical, thoracic and lumbar vertebrae, or with the relative length of the cervical, thoracic and lumbar cord,[2] it will be found that the relative frequency in the different regions runs fairly parallel with the number of vertebrae and the length of the spinal cord in the cervical, thoracic and lumbar regions. (Table 3).

However, if the figures are analyzed for the perineurial fibroblastomas and the meningiomas, the relations are seen to be entirely different from the meningiomas (Table 4).

TABLE 1

The relative frequency of 267 extramedullary tumors of the spinal cord

	EXTRA-DURAL	INTRA-DURAL	EXTRA-DURAL AND INTRA-DURAL	TOTALS
Perineurial fibroblastoma	5	48		53
Meningeal fibroblastoma	4	75		79
Sarcoma	22	9		31
Angioma Hemangioblastoma	4	5		9
Fibroma	4	10		14
Neurofibroma (von Recklinghausen)	1	3	1	5
Dermoid	0	4		4
Lipoma	1	3	2	6
Ependymoma	0	11		11
Cyst	2	1		3
Ganglioneuroma	2	0		2
Chondroma Herniation of nucleus pulposus	27	0		27
Granuloma	0	1		1
Metastatic and secondary	11	2	1	14
Unclassified	0	8		8
Totals	83	180	4	267

Table 4 demonstrates this interesting fact: The relative frequency of the perineurial fibroblastomas at various levels of the vertebral canal closely parallels the number of cervical, thoracic and lumbar vertebrae and also the relative length of the cervical, thoracic and lumbar cord (Table 5). The perineurial fibroblastomas are derived from nerve roots, and it appears as if no special root or roots were the sites of predilection of these growths.

When the figures for the meningiomas are studied from the same point of view, it is at once apparent that the incidence of this type of growth in

[2] The relative lengths of the cervical, thoracic and lumbar spinal cord are those given by Ravenel (10).

the thoracic region is much higher than should be expected from the relative length of the thoracic cord. To a certain extent also the angiomas occur relatively often in the thoracic region (see Table 5). One is led to suspect, therefore, that there is some other factor which will explain the frequency

TABLE 2

Vertebral levels of 267 extramedullary tumors

VERTEBRAL LEVEL	EXTRADURAL	INTRADURAL	INTRADURAL AND EXTRADURAL	TOTALS
Cervical I to III	4	12		16
Cervical IV to VIII	17	28	2	47
Thoracic I to III	10	24	1	35
Thoracic IV to VIII	25	48		73
Thoracic IX to XII	12	36	1	49
Lumbar I to III	6	20		26
Lumbar IV to V	8	12		20
Sacral	1			1
Totals	83	180	4	267

TABLE 3

VERTEBRAE	LENGTH OF SPINAL CORD (RAVENEL)	TUMORS
Cervical 7 = 29%	10 cm. = 23%	16 = 24%
Thoracic 12 = 50%	26 cm. = 58%	157 = 59%
Lumbar 5 = 21%	8.5 cm. = 19%	47 = 18%

TABLE 4

Vertebral levels of 172 tumors

VERTEBRAL LEVEL	PERINEURIAL FIBROBLASTOMA	MENINGEAL FIBLOBLASTOMA	ANGIOMA	SARCOMA
Cervical I to III	5	4	0	2
Cervical IV to VIII	9	6	1	5
Thoracic I to III	6	13	2	3
Thoracic IV to VIII	10	31	3	9
Thoracic IX to XII	14	21	2	7
Lumbar I to III	8	4	0	3
Lumbar IV to V	1	0	1	2

of the meningiomas in the thoracic region. What this factor may be is to a considerable degree speculative, but it appears probable that it is in some way related to the development of the spinal membranes.

In a study of the development and differentiation of the membranes of the spinal cord, Hochstetter (6) has shown that the anlage of the dentate ligament appears very early, that, in an early stage, it is in connection both

with the primitive perichondrium and with the cells that are to form the pia mater and that these cells stream in between the groups of cells that are to form the spinal ganglia. The spinal ganglia are first inside of the anlage for the dura, but in the development of the spinal membranes, the ganglia gradually move outwards to what are to be the intervertebral foramina. At a time when the cervical and first thoracic ganglia and also the lowermost thoracic and the lumbar spinal ganglia are already outside of the cell groups which are the primitive dura, the thoracic ganglia (T II to T XI) are still definitely intradural (Figs. 1 and 2). Now it is suggestive and at least a remarkable coincidence that the meningiomas occur with greatest frequency in this part of the spinal membranes, as shown in Table 6 in which the meningeal tumors of our series are grouped according to the sensory levels at which they were found.

3. The relation of extramedullary tumors to the dura, arachnoid and pia mater.

TABLE 5

The frequency of tumors compared to the number of vertebrae and to the relative length of the cervical, thoracic and lumbar cord

VERTEBRAE	LENGTH OF SPINAL CORD (RAVENEL)	PERINEURIAL FIBRO-BLASTOMAS	MENINGEAL FIBRO-BLASTOMAS	ANGIOMA	SARCOMA
Cervical . 7 = 29%	10 cm. = 23%	14 = 26%	10 = 13%	1 = 11%	7 = 23%
Thoracic .12 = 50%	26 cm. = 58%	30 = 57%	65 = 82%	7 = 78%	19 = 61%
Lumbar . . 5 = 21%	8.5 cm. = 19%	9 = 17%	4 = 5%	1 = 11%	5 = 16%

As shown in Table 1, the growth was intradural more than twice as often as extradural. In this connection (and as has already been mentioned), it must be remembered that the series of cases on which these figures are based were in patients who were operated upon. A large number of patients with metastatic tumors were not subjected to operation and therefore do not appear in the figures.

The relation of intradural tumors to the arachnoid was particularly studied, but only those cases are included in Table 7 in which the relation of the growth to the arachnoid was carefully investigated as soon as the dura had been incised. I have made it a rule to use care when the dura is incised so that, whenever it is possible, the arachnoid sac is not opened. By this procedure one can see a growth attached to the outer or inner surface of the arachnoid or whether it is attached to the pia mater with non-adherent arachnoid over it. Therefore one is able to determine whether the growth lies outside or inside of the arachnoid and whether it is adherent to that membrane. When a growth is adherent to the inner surface of the dura but not to the arachnoid, one can raise the growth away from the unopened arachnoid by elevation of the dura; when the growth is adherent to the outer surface of the arachnoid but not to the dura, the

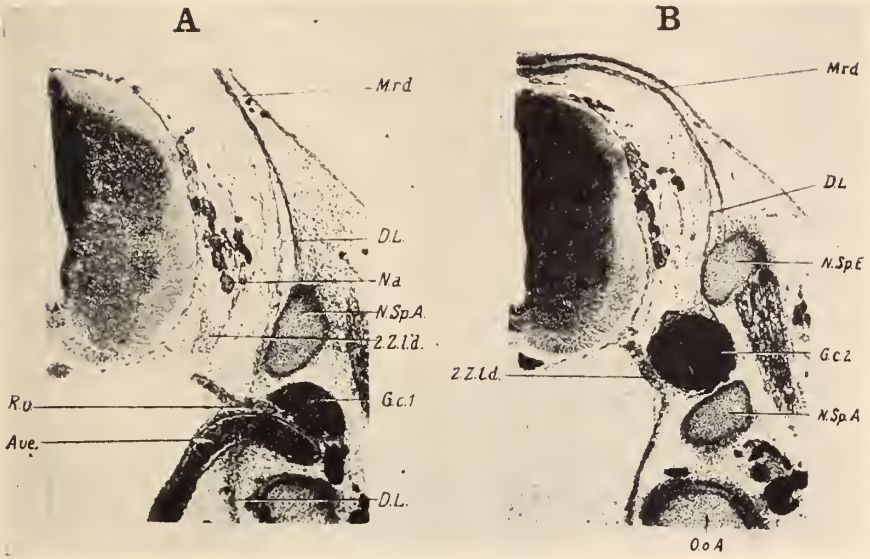

FIG. 1. Transverse section through the spinal cord of an embryo of 21.66 mm. at the level of the first cervical (A), left, and second cervical (B), right, ganglion. In A, the first cervical ganglion is entirely extradural; in B, the second cervical ganglion is to a considerable extent extradural (×30) (Hochstetter). G.c., cervical ganglion; D.L., dura mater-lamella.

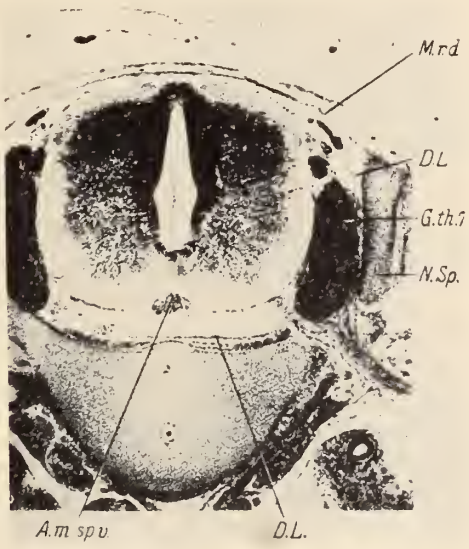

FIG. 2. Transverse section through the spine and spinal cord level of the seventh thoracic spinal ganglion of the same embryo as in Fig. 1 (×30) (Hochstetter). The ganglion is still intradural.

growth is seen to lie outside of the arachnoid sac; when it is adherent to the inner surface of the arachnoid it may be seen within the unopened arachnoid sac, etc. In some of the cases, however, the growth may be extraarachnoid but surrounded by arachnoid so that it appears to lie within that membrane. This is similar to the relation met with in the cranial meningiomas. The large majority of cranial tumors appear to originate from the inner surface of the dura and to carry the arachnoid with them

TABLE 6

	CERVICAL							
	I	II	III	IV	V	VI	VII	VIII
Number of cases	2	1	1	0	1	2	1	2

	THORACIC											
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
Number of cases	2	5	6	8	5	5	7	6	7	6	5 (?)	3 (?)

	LUMBAR				
	I	II	III	IV	V
Number of cases	2	1	1	0	0

TABLE 7

The relation to the membranes

	EXTRA-DURAL	INTRADURAL		SUBPIAL
		Extra-arachnoid	Intra-arachnoid	
Meningeal fibroblastoma	4	6	15	1 (?)
Perineurial fibroblastoma	4	3	17	0
	8	9 = 22%	32 = 78%	
Of 41 intradural growths		9 = 22%	32 = 78%	
Of 21 intradural meningiomas		6 = 29%	15 = 71%	
Of 20 intradural perineurial fibroblastomas		3 = 15%	17 = 85%	

as they bury themselves in the brain. In a very few instances of small meningiomas over the convexity in one or other cerebral hemisphere, or underneath a frontal lobe, I have been able to ascertain that the growth was subarachnoid, i.e. was not surrounded by a layer of arachnoid. In most of the cranial meningiomas, however, it is impossible to arrive at a conclusion whether the growth is primarily extra or intraarachnoid, and it is fortunate that in the spinal growths the exact relation between tumor and arachnoid can often be definitely seen.

In 50 cases of perineurial fibroblastoma and meningeal fibroblastoma, the relation of the growth to the arachnoid is shown in Table 7.

The situation relative to the spinal membranes in which I have observed meningeal growths are illustrated in Figure 3.

The figure shows that meningiomas unattached to nerve roots was met with: (a) on the outer surface of the dura attached to that membrane; (b) adherent to the inner surface of the dura outside of and without any attachment to the arachnoid; (c) springing from the outer surface of the arachnoid without any connection with the dura; (d) adherent to the inner surface of the arachnoid but not attached to the pia mater; (e) within the

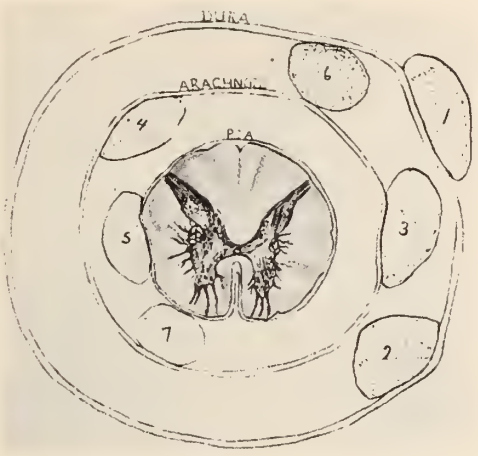

FIG 3. The relation of spinal meningeal fibroblastomas to the membranes (diagrammatic). 1, extradural adherent to dura; 2, intradural adherent to inner surface of that membrane but not to arachnoid; 3, extra-arachnoid adherent to outer surface of arachnoid but not to dura; 4, intra-arachnoid adherent to inner surface of that membrane but not to pia; 5, adherent to pia but not to arachnoid; 6, adherent to inner surface of dura and to outer surface of arachnoid; 7, adherent to inner surface of arachnoid and to outer surface of pia.

subarachnoid space attached to the surface of the cord (pia mater) but not to the membranous arachnoid. Recently I have seen a case in which it seemed probable that the meningioma was subpial.

If the spinal meningiomas were derived from cells of the arachnoid which had become adherent to or had grown into the dura and had there developed into actual newgrowths, it would be difficult to explain why such a growth should be met with *outside* of the dura, or adherent to the *inner* surface of the dura without any demonstrable connection with the arachnoid. Any explanation that will not suffice for the genesis of spinal meningeal growths must likewise be inapplicable to the tumors of the same category within the cranial cavity.

According to investigations made many years ago by His and by Köl-

liker (7), the meninges are developed from the primitive mesenchyme around the neural tube. The term mesenchyme may be used no matter whether it is believed that the cells of the middle germinal layer give rise to the meninges or whether cells derived from the neural crest contribute to the formation of the leptomeninges.

According to Weed (11), the dura and the arachnoid (or at least its outer layer) differentiate together through the early condensation of groups of cells in the perimedullary mesenchyme rather than that the outer condensation of cells is the precursor of the dura alone. On the other hand, Hochstetter has recently shown that in the spinal canal the perichondrium and outer layer of the dura develop from one group of cells and that at an early stage there are cells from the primitive pia mater that can be traced to the primitive perichondrium.

At this early stage, it may well be that cells that should have become grouped with those that were to form the arachnoid had lost their proper affiliation and alignment and had remained with cells which were predestined to develop into pia or dura mater. On this basis, (the Cohnheim theory of the origin of tumors), it would be possible to explain why a growth which reproduces the structure of the arachnoid may be met with in a situation not connected with that membrane. This would make it clear why the spinal meningiomas are encountered in the various situations I have described, and would lead to the conclusion that the meningiomas are developed from misplaced mesenchymal cell rests which may become differentiated in abnormal situations to form heterotopic malformations.

4. The gross effects of tumors upon the cord, nerve roots and membranes.

During many years, I have made notes regarding the gross effects of extramedullary tumors upon the spinal cord, both as regards the dislocation of the cord by the growth and the depression in the cord produced by it. From this point of view, it is important to distinguish between growths of soft consistency such as the majority of perineurial fibroblastomas, many of the ependymomas, the lipomas, dermoids and extradural and intradural cysts on the one hand, and the growths of firmer consistency, such as most of the meningiomas, the pure fibromas, the hemangioblastomas and the extradural chondromas and nucleus pulposus herniations, on the other hand. The firmer the consistency of a growth, the more apt it is to cause an angulation of the cord at the affected level, and the more frequent a deep depression in the spinal cord due to the tremor. In spite of its slow growth, the meningioma is very apt to cause a marked dislocation of the cord especially when it is ventrally or dorsally situated, and the more apt it is to cause a marked angulation of the cord. As shown in the accompanying composite diagram (Fig 4), made from sketches at the operating table, the meningioma causes cord angulation and a depression in the cord substance which is much more marked than one sees in the perineurial fibroblastomas and the other growths of softer

consistency. The effect upon spinal nerve roots is similar to that upon the cord, one seldom sees nerve roots stretched over the surface of a perineurial fibroblastoma that are as tense or as much angulated as one seems in the firm hard meningeal growths. It is often impossible to pull a meningioma out from under a nerve root stretched over it without undue force, while this is usually possible in the case of a perineurial fibroblastoma. As many of the meningiomas are fixed to the dura by a firm adhesion and are held in position by one or several nerve roots stretched over the growth, it follows that the meningioma is usually more fixed and immovable than the perineurial fibroblastoma. The fact that so many of the meningiomas are fixed in position will explain to a considerable extent, the deep depression in the cord that is so often observed.

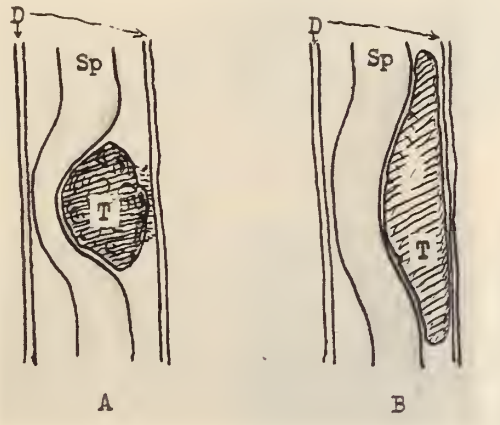

FIG. 4. The mechanical effects of extramedullary spinal cord tumors. A, a meningioma; B, a perineurial fibroblastoma (diagrammatic). D, dura; Sp, spinal cord; T, tumor. A composite of the operative sketches of a large number of cases. Marked angulation of the cord is more apt to occur in the firm, hard meningioma than in the softer perineurial fibroblastoma.

5. The writer has kept a record of the vascularity of the paravertebral soft tissues and of the bone overlying extramedullary spinal cord tumors. What is here referred to is not the presence of any especial large bleeders but the general oozing from the soft tissues when they are divided and the bleeding from the bone while the laminectomy is being performed. A study of the records has led to the conclusion that increased vascularity of the soft tissues and of the bone is very frequent in vascular tumors such as many meningiomas, most of the ependymomas, the hemangioblastomas and vascular extradural growths. From the increased bleeding met with in the separation of the muscles from the bone and in the removal of the spinous processes and laminae during the laminectomy, one can often gain an idea of the vascularity of the spinal growth and therefrom fre-

quently suspect the pathological nature of the growth. This increased vascularity of the soft tissues and bone appears to be similar, although

FIG. 5. X-ray showing the enlargement of the interpedicular space of the twelfth thoracic vertebra in a case of extramedullary tumor at that level.

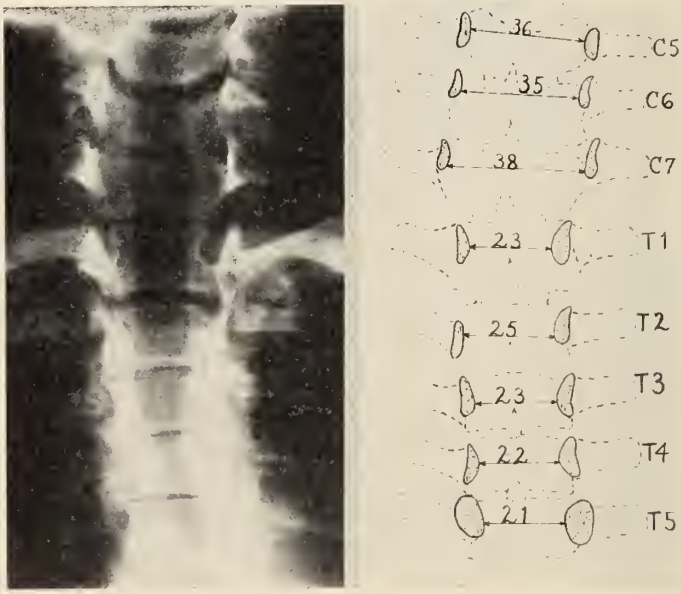

FIG. 6. X-ray showing enlargement of the interpedicular spaces and atrophy of the pedicles of the three lower cervical and four upper thoracic vertebrae in a case of large extradural and intradural lipoma.

much less in degree, to what is observed in the soft tissues of the scalp and the bone in the intracranial meningiomas.

6. The changes in the bony structures of the spine at the level of a spinal cord tumor have been recently described by the writer with Dr. C. G. Dyke (3). Roentgen studies of the vertebrae in a large series of spinal cord tumors appear to show that measurable enlargement of the vertebral canal is especially apt to occur in large soft tumors. Enlargement of the canal as shown by interpediculate measurements and often visible without measurements occurs regularly in the so-called giant tumors of the conus and cauda equina (most of which are ependymomas), in extradural and intradural lipomas and cysts (Figs. 5 and 6). In these types of tumor, the enlargement of the canal extends over two to five vertebrae.

An enlargement of the interpediculate spaces of one or two vertebrae is not rare in the perineurial fibroblastomas but surprisingly enough is quite unusual in the meningeal fibroblastomas. With the enlargement of the canal there is usually an atrophy of one or of a number of the pedicles. These alterations in the bony structures, visible on roentgen films of the affected vertebrae—are quite different from the erosion or destruction of parts of the vertebrae which occurs so frequently in metastatic spinal extradural malignant disease.

SUMMARY

1. An analysis of the gross features of 267 primary and secondary extramedullary tumors of the spinal cord showed that, for the entire group, the frequency at different levels corresponded to the relative lengths of the cervical thoracic and lumber spinal cord.

2. The relative frequency of the perineurial fibroblastomas at various levels closely paralleled the number of cervical, thoracic and lumbar vertebrae and also the relative lengths of the cervical, thoracic and lumbar cord.

3. The incidence of the meningeal fibroblastomas in the thoracic region was much higher than should be expected from the relative length of the thoracic spinal cord.

4. It is suggested that the frequency of the meningeal growths in the thoracic region is related to the development of the spinal membranes.

5. The meningeal fibroblastomas were most often encountered within the arachnoid, but they were found both outside and inside of the dura and of the arachnoid. If cells from the primitive mesenchyme,—that should have become grouped with those that were to form the arachnoid,—had lost their proper affiliation and alignment and had remained with the cells which developed into pia or dura mater, it would be possible to explain why a growth which reproduces the structure of the arachnoid may be met with in a situation not connected with that membrane.

6. There is an increase of vascularity in the soft paravertebral tissues and the bone in vascular tumors of the spinal cord.

7. The changes produced in the vertebrae and in the spinal cord by tumors are described.

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EVOLUTION OF THE TREATMENT FOR ABSENT VAGINA

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The study of the evolution of procedures for the cure of any disturbance is a fascinating one. In the present instance it can be followed from the first recorded attempt to establish an artificial vagina by Dupuytren in 1817 to the present day.

Absence of the vagina is a fairly common malformation found in otherwise perfectly normal feminine individuals. The vulva appears entirely normal. On separating the labia, a dimple or small blind pouch in the region of the hymen, varying in depth from one-quarter to three centimeters, is usually found, although recently I have encountered a case where no depression was present. Rectal examination, as well as exploratory laparotomies, have shown that in almost every instance the uterus is represented by a small, solid, muscular rod (*uterus rudimentarius solidus*) with tubes and ovaries. The tubes may or may not be canalized. The ovaries are usually normal, and corpora lutea have repeatedly been found.

I have encountered more than thirty of such individuals and of these, twelve have been subjected to hormonal studies. In only two, (one of these was over forty years of age) was no positive, feminine hormonal blood or urine cycle determined. In five patients in whom a complete study of blood and urine over a period of thirty days was made, the variations which are found in average groups of females were encountered. The lowest monthly excretion was 820 I.U., the highest, 4200 I.U. The average as determined on groups of fertile menstruating women is 1500 I.U. $\pm$300.

In this group of over thirty females with absence of the vagina, the great majority showed normal feminine habitus. One was acromegalic; several were handsome and attractive. The sex urge in both the married and unmarried women of this group was definitely within normal range. Young, unmarried women who had previously been informed of their malformation and inability to become married, unless some intervention was practiced, had one and all developed an inferiority complex and showed signs of unhappiness and unrest. Two of the married women were threatened with divorce and the marriage of one had been annulled because of *impotentia coeundi*.

Because of the situations arising from absence of the vagina, as well as the fact that these individuals were definitely females, I have never felt any hesitation in attempting to relieve them of their disability nor have I ever

had more gratifying results from any surgical or other intervention. These results now date back to 1927 and have proved permanent.

The afflicted individuals rarely are aware of their malformation until the age of puberty has passed. At that time local examination will disclose the situation. I have encountered two patients who received so-called "endocrine therapy" over several years, mainly injections of estrogens, because of the accompanying amenorrhea; absence of the vagina being discovered at a later date.

As mentioned in the introductory paragraph, the first recorded attempt to establish an artificial vagina was practiced by Dupuytren in 1817. This surgeon burrowed into the urethrorectal septum and inserted plugs, with the hope that epithelialization would take place. The result was disappointing. Heppner, in 1872, introduced skin flaps, the canal later contracting. Attempts by others to line a preformed canal with Thiersch grafts likewise failed. Gersuny, in 1897, transplanted the anterior wall of the rectum with passable result. Sneguireff isolated the lower portion of the rectum, establishing a sacral anus and transplanting the lower portion of the rectum into the vaginal opening. This operation was soon discontinued.

In 1904, Baldwin suggested the first satisfactory operation which he actually carried out in 1907. This operation consisted in isolating a loop of the ileum, re-establishing the continuity of the intestinal canal, and then pulling down the double loop of intestine between urethra and rectum. The resulting double barrel vagina was later made into a single canal by applying a crushing clamp. Such an operation could only be practiced by skillful abdominal surgeons, and in seventy-nine cases collected by Daniel, showed a mortality of seventeen and a half per cent. This recorded mortality appears to be too small as I am aware of several fatalities which were never reported in the literature. Mori, about the same time, devised an operation similar to that of Baldwin, except that the loop of intestine utilized was single and not double barreled.

Because of the high mortality following the Baldwin operation, Poppoff, Schubert, and others devised a difficult but distinctly less dangerous procedure in which the lower portion of the rectum was liberated and transplanted into the urethrorectal septum, the continuity of the rectum being re-established by liberating the lower sigmoid from below and uniting it with the remaining anal portion of the rectum. The mortality in this procedure was three deaths in fifty-three cases. Rectovaginal fistulae, incontinentia alvi and other disagreeable sequelae resulted.

In consequence of the gravity of the intraabdominal and rectal transplantations, Jewett (1904), Graves (1921), Charbonnel and Faveau (1921), Fraenkel (1924) devised less dangerous but also less effective methods which consisted in utilizing pedicle flaps obtained from the hymen, fourchette, and vulvar skin which were liberated, after a canal had been pre-

formed, their edges united by suture and then invaginated into the canal by means of packing or plugs, the mucosa or skin surfaces facing the newly formed cavity. In numerous instances annoying hair growth developed and the canals showed a tendency to atresia and obliteration. This tendency could only be overcome by continuous wearing of a plug.

In 1925 several cases of absence of vagina presented themselves. Naturally, my interest was aroused because of the unfortunate situation of these patients. I could not make up my mind to perform the dangerous Baldwin or Schubert procedures for a condition which in itself did not endanger life. It was at this time that Geist and I, both of us familiar with the great increase in vitality obtained by means of tubular flaps suggested by Gillies for replacing disfiguring war injuries, planned and executed a new technic, now generally known as the "satchel-handle technic," in which first skin flaps were obtained from the inner, hairless regions of the thighs, endowed with great resistance by preliminary tubularization, the distal pedicle gradually cut, the flap eventually re-opened, and used to form a complete skin covering for the newly formed canal. This operation was performed successfully upon six cases, the results proving permanent and satisfactory, although plugging was necessary for several months after establishment of the new vagina. While this operation, both in our hands and in those of others, proved satisfactory, it entailed a three-stage operation with at least eight weeks of hospitalization. Several surgeons since the publication of our report have tried to simplify the procedure by endowing skin flaps with resistance by means of gradual liberation and concentration of their blood supply through the proximal pedicle (Herman Grad).

The time for any intervention is preferably between eighteen and twenty years. A number of patients had already planned to marry.

I had always been impressed by the ease with which it was possible to separate rectum from urethra after incision of the hymen and superficial fascia. Those who have reported any operation for establishing an artificial vagina will have noted that the septum can be separated with two or three sweeps of the finger up to the peritoneal reflexion.

In the last few years, with the aim of simplifying the establishment of an artificial vagina, numerous improved attempts to utilize Thiersch or Wolf grafts, either sewed to or applied to the surface of an appropriate plug by means of mastic paste, were attempted with encouraging results although all attempts to use this type of technic in the previous century had resulted in failure. A further advance was made by completely burying such plugs in the preformed canal by means of obliterating circular sutures and leaving them *in situ* for weeks or months before re-opening the canal. But even this advance in many instances resulted in subsequent atresia.

In 1935 a case presented itself in which there was a deep dimple, apparently the result of vigorous attempts at coitus. As is well known to

those familiar with this situation, such attempts usually end in dilatation of the urethra, coitus taking place through this canal, sometimes resulting in permanent incontinence of urine or deep tears of the urethra (Schubert). In the instance just quoted, however, the efforts had resulted more successfully. Any one familiar with the case with which the septum between urethra and rectum in absence of the vagina can be separated by the introduction of two fingers after the hymeneal membrane has been incised, must have been impressed by the resilience and softness of these tissues. This had repeatedly struck me as encouraging. In this first case, therefore, I had the patient introduce heavy glass tubes, first of small diameter, later increasingly larger, and to my surprise and gratification, within a few weeks a canal, seven and a half centimeters in length, was developed. Since then eight further cases have been completed by this simple, non-operative, ambulatory method of treatment. Some of the cases (they will be reported in more detail in the New York State Journal of Medicine) were in unmarried individuals who have not practised coitus, and yet these canals after being fully established, remain lined with soft, yet resistent mucosa, which has only a moderate, non-irritating secretion, retain their full length, and show no tendency to obliteration or stenosis. A tenth case now in process of treatment, showed an absolutely flat membrane from labium minus to labium minus, only a short distance between urethral meatus and fourchette, with a more resistent septum than has been usually encountered. In spite of these difficulties, the urethra has been successfully avoided and after a prolonged use of the intubation method, a canal now four and a half centimeters deep, has been established, but there is every prospect that eventually adequate depth and dimensions can be reached. The majority of the patients treated by the intubation method are now happily married.

In this brief review of a very specialistic but interesting condition, it becomes apparent that our predecessors in the pre-Listerian days, were limited to simple and superficial methods of intervention which were largely nullified by the presence of infection and crudeness of technic, as shown by the fact that in more recent years, slight variations in their technic have resulted in successes, the results, however, entailing certain disadvantages. Then came an era in which difficult and dangerous interventions were practised with greater impunity because of aseptic technic but, in my opinion, the Baldwin and Schubert operations are definitely contra-indicated because of the dangers involved. A return to simplification has become manifest in the last two decades, but these simpler operations likewise entail hospitalization and scarring in the neighborhood of the vulva. Therefore I have no hesitation in strongly urging the profession to employ the non-operative method which I have developed, a method which is ambulatory, which produces no scars, and which, so far, has proved uniformly successful in establishing *potentia coeundi* and in restoring the self-respect and happiness of the afflicted individuals.

OBSTRUCTION OF THE TRANSVERSE COLON IN A DIAPHRAGMATIC HERNIA

With a Note on Dr. Lilienthal's Contribution to the Two-Stage Operation

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Obstructions of the colon by intrinsic lesions are encountered very frequently; most of these are due to malignant tumors. Occasionally a benign tumor, a lipoma for example, will cause obstructive symptoms.

One of the most frequent extrinsic causes of obstruction is the volvulus of the descending colon, usually occurring in the presence of an abnormally mobile descending colon or sigmoid flexure.

While the tumors are usually encountered in the age groups above fifty, volvulus of the intestine is usually caused by a congenital anomaly and may occur in any age group.

It is impossible to enumerate here all the other pathological conditions, either intrinsic or extrinsic, which may cause an obstruction of the colon.

The case reported herewith undoubtedly presents a rare cause of colonic obstruction. In a personal experience with intestinal surgery extending over nearly forty years I have never encountered a similar condition.

For this reason a case which I observed recently seems of sufficient interest to warrant a brief report.

CASE REPORT

History (Adm. 404860). C. C., age 23, was admitted to the Surgical Service of The Mount Sinai Hospital on February 19, 1937.

The patient stated, upon his admission to the hospital, that he had noticed cramp-like pains in the left upper quadrant for the past two days and had vomited frequently. There had been no spontaneous bowel movement and no passage of flatus since the onset of his illness. Enemas had been ineffectual.

When questioned about previous illnesses he stated that he had sustained multiple stab wounds of the chest and arms eleven months before. At that time he was admitted to the Emergency Ward of another hospital complaining of pain on respiration and pain in the lung.

A report from the hospital to which he was admitted at this time stated that the patient had sustained multiple lacerations in the left chest anteriorly and posteriorly. There was a deeply incised wound situated two inches above the lower third of the sternum and extending down to the bone. Another laceration ran in the anterior axillary line to the tenth intercostal space and two other lacerations were noted over the left scapula. X-ray examinations at the time of the injury failed to show any evidence of a lesion of the heart or lungs. Examination showed hyper-resonance

and diminished breath sounds over the left lung posteriorly. The heart appeared pushed over to the right. The left upper quadrant of the abdomen was spastic and tender. There was no costovertebral angle tenderness and no obliteration of liver dullness was noted.

He was discharged from that hospital and was perfectly well until two days before his admission to The Mount Sinai Hospital.

Examination. The patient was a well-developed and well-nourished Porto Rican male, who was in bed with his thighs flexed, groaning and rolling about with pain. There was neither dyspnea nor cyanosis, the pulse was of good quality and his color was good. A number of healed stab wounds were present over the lower sternum, left hypochondrium and left shoulder. Examination of the lungs was negative except that the left leaf of the diaphragm was elevated and did not move well with respiration. The heart was deviated somewhat to the right with its apex situated about three inches from the left border of the sternum and right margin two inches from the right border of the sternum. The abdomen was moderately distended but soft, and did not show any visible peristalsis. There was some tenderness on deep pressure in the right upper quadrant.

The clinical diagnosis was intestinal obstruction of unknown origin.

X-ray examination (February 19, 1937), showed the following: "Marked distention of the large bowel is present particularly at the level of the transverse colon. No gas is seen in the large bowel distal to the splenic flexure. There is a small amount of air in the ileum. Fluid levels are seen when the patient stands up."

A barium enema made subsequently (February 20, 1937) showed the following: "There is a partial obstruction to the ingestion of barium in the upper portion of the descending colon. At this point the colon is narrowed and the entire splenic flexure is displaced to the flank and upward. The appearance of the narrowed cecum and of the descending colon suggests compression by an outside mass, but the possibility of neoplasm cannot be definitely excluded. There is considerable distension of the large bowel proximal to the mass."

On the following day, the symptoms not having subsided, a cecostomy was performed (Dr. A. S. W. Touroff) under spinal anesthesia for suspected tumor at the splenic flexure of the colon with acute intestinal obstruction.

Operation. The peritoneal cavity was entered through a 3½-inch McBurney incision and a large amount of clear odorless fluid was evacuated by suction. The cecum was found to be tremendously distended. In order to visualize the caput coli the incision was extended upward. The cecum was emptied by means of a trocar and cannula and large sized catheter was then introduced and anchored in the cecum by a chromic catgut stitch. The bowel was inverted above the tube by a few purse-string sutures. Several packings were placed around the tube which was brought out through the wound. Following this cecostomy, the intestine drained well, the vomiting ceased and the distention subsided within a few days.

Barium enema examination, made on March 4, 1937 (two weeks after the cecostomy), did not throw any further light on the cause of the obstruction. The report reads as follows: "There is an irregular stenosing lesion in the proximal loop of the splenic flexure with marked obstruction. There is also evidence of adhesions from the descending colon at the splenic flexure to this lesion, with narrowing but only incomplete obstruction. The appearance at the present time suggests strongly an intrinsic obstructing lesion of the proximal loop of the splenic flexure."

Thus, with a preoperative diagnosis of tumor in the transverse colon, possibly of a benign nature, I explored this patient on March 8, 1937, under avertin and gas anesthesia. The transverse colon was exposed through a six inch left rectus incision, but no tumor could be felt. However, it was evident that the splenic flexure was caught in a diaphragmatic hernia. In order to expose the lesion properly, a

transverse incision through the left rectus was added to the longitudinal incision. It was now possible to free the adhesions between the colon and hernial sac and to deliver the splenic flexure completely, and replace it into the abdominal cavity. There were still some adhesions of the omentum which were divided between clamps. The mesentery of the colon showed slight inflammatory thickening. This part had evidently been situated at the neck of the hernial sac. After the contents of the hernia had been freed and brought down into the abdominal cavity the large opening in the diaphragm was closed by five interrupted chromic catgut stitches. The abdomen was closed in layers, without drainage. The patient made an uninterrupted recovery. The cecostomy tube continued to drain well after the second operation and was removed on March 21. The next day the patient had a normal bowel movement and the cecostomy drainage diminished rapidly and stopped completely after a few days. An X-ray examination made on April 3 showed that the splenic flexure was now distinctly below the diaphragm. There was a redundancy of the splenic flexure and slight irritability and spasm of the descending colon. No other abnormalities were noted.

The patient was seen in the Follow-Up Clinic on April 21, 1937, and again one and a half years later (September 3, 1938). Both wounds were firmly healed and the patient felt perfectly well.

DISCUSSION

The cause of the colonic obstruction in this case was not diagnosed correctly until the second operation. The correct diagnosis might have been made before the operation, however, if the evidence had been weighed properly and if sufficient stress had been laid by us on the previous trauma (multiple stab wounds of the chest). As it happened, the error in the preoperative diagnosis (obstruction due to tumor rather than to a diaphragmatic hernia) did not cause any erroneous operative interference. We would have followed the two-stage procedure even if the correct diagnosis had been made on admission.

This brief report of a two-stage operative procedure gives me an opportunity to discuss the value of so called stage operations and Dr. Lilienthal's important contribution to these procedures. It may surprise the younger surgeons to learn that over thirty years ago Dr. Lilienthal presented the subject of stage operations under the title of "The Two-Stage Principle in Operative Surgery,"[1] before the N. Y. Surgical Society. The impression is gained that stage operations are of rather recent date and were practically unknown to the surgeons of the older generation.

There is a grain of truth in the idea that stage operations are a recent addition to surgical technique. While this whole subject was elucidated and discussed in Dr. Lilienthal's paper and while, as we shall see, very few new indications have been added, since his presentation of the subject, it took many years to popularize these procedures; "The mills of the gods grind slowly." Many surgeons felt that to resort to stage procedures

[1] Howard Lilienthal, "The Two Stage Principle in Operative Surgery," Ann. Surg., 51: 31, 1910.

might be wrongly interpreted by the patient or his relatives as a lack of courage on the part of the surgeon, and thought that their reputation might hence suffer. Thus, for many years, stage operations were not resorted to, except in rare instances. The tendency of the surgeons of the older generation was to finish the operative procedure in one stage and not to extend the convalescence over many months.

Whenever I have heard a surgeon say, "I am willing to take the chance," before proceeding with a life endangering operation, I have asked myself, "Who takes the chance, the patient or the surgeon?" It is the high mortality of many operative procedures which gradually forced the popularization of these stage procedures. In fact it seems that the laity showed better judgment than some members of the medical profession. For instance, during an extensive personal experience in goitre surgery I noticed that many patients insisted on stage operations. They preferred a longer period of operative recovery with the inconveniences of repeated anaesthesias to the inherent risks of operations in one stage.

Let us see what Dr. Lilienthal has to say on this subject in his original paper. He starts his paper with the motto: "Not how skillful, but how safe." These are indeed wise words from a man whose courage was never doubted by any member of his staff. He then discusses the importance of shortening the duration of the anaesthesia, the rôle of excessive hemorrhage during an operation, and the element of shock in causing death. He defines very clearly the indications for stage operations under the following seven groups:

1. For intracranial disease.
2. For intrapulmonary disease.
3. For obstruction of the bile passages.
4. For obstruction at the pylorus.
5. For malignant disease of the rectum.
6. For hypertrophy of the prostate.
7. For suppuration in the kidney.

He gives the indications for stage procedures in these groups in his usual lucid manner of presenting new facts and of attracting the reader's interest by his original approach.

Naturally some of the indications for two-stage operations have been changed by improvements in technique. Today, for instance, stage operations in cranial surgery are rarely performed, although advocated by some surgeons in brain abscess and by others for certain intraventricular tumors.

It seems that in surgery of the lungs two-stage procedures are not used nearly as frequently as they were twenty years ago. With modern improvements in anaesthesia and technique it is apparently quite safe to perform formidable operations, for instance a lobectomy, in one-stage.

Dr. Lilienthal deals with the subject of operations for the relief of biliary obstructions in the following interesting paragraph:

"In prolonged icterus, especially when there are cirrhotic changes in the liver, even slight operative interference is apt to be followed by fatal recurrent or secondary hemorrhagic oozing. To be sure, a few precautions may be taken to shorten the coagulation time of the blood, such, for example, as the injection of alien serum before the operation. From personal experience, however, I am of the opinion that in operations of magnitude the danger of hemorrhage continues long after the good effects of the alien serum have disappeared. The safer mode of procedure, then, when deep chronic jaundice is present, is to employ serum or other therapy and to operate by the shortest and simplest possible method merely for the relief of cholaemia, reserving the removal of the cause of obstruction until a later operation."

How true is this statement written as it was thirty years ago, at the present time! Replace the words "alien serum" by the words "blood transfusion" and add the new hemostatic Vitamin K and the paragraph is brought up-to-date. For, in spite of all modern improvements in the pre-operative preparation of these patients, it is still a good practice in cases of deep and protracted jaundice due to stones in the common bile duct to remove the stones and postpone cholecystectomy to a later date. Neither blood transfusion nor Vitamin K are a complete safeguard against the postoperative hemorrhage which often follows cholecystectomy in the deeply jaundiced patients. Naturally with the advent of blood transfusion the indications for two-stage operations in jaundiced patients are not nearly as often encountered during the last twenty years as when Dr. Lilienthal wrote this paragraph.

Blood transfusion was practically never used in 1910 as the only available method was the direct transfusion from artery to vein. I remember that period very well, as I served as an adjunct at The Mount Sinai Hospital during the years 1907 to 1914 on the service of Dr. Lilienthal's colleague, Dr. Arpad Gerster. In that period not more than half a dozen transfusions per annum were given. With the advent of the citrate method the number of blood transfusions given at The Mount Sinai Hospital have increased from year to year until they reached 1910 transfusions in 1939. While it must be granted that some of these transfusions may not have been strictly indicated, their beneficial effect and the revolution which they have brought to medicine and surgery cannot be overestimated.

I hope that I have not transgressed too far. Let us return to the subject of stage operations in gall bladder surgery. Improvements in technique during the last thirty to forty years have made cholecystectomy in patients without jaundice a very safe procedure. Thus, cholecystostomy is rarely resorted to now, except in very old or feeble patients. Forty

years ago the mortality after simple cholecystectomy was very considerable and here again Lilienthal's remarks on this subject make interesting reading.

In large pericholecystic abscesses with sepsis and high fever it is still a good practice simply to drain the abscess and possibly also the gall bladder and then remove the gall bladder after the acute symptoms have subsided.

In liver abscess without adhesions to the abdominal wall it is most advisable to pack off the abdominal cavity, after the peritoneum has been incised and to wait with the drainage of the abscess until secondary adhesions have formed to protect the abdominal cavity against infection.

In the fourth paragraph of his paper, Dr. Lilienthal discusses the two-stage operation in malignancies or inflammatory tumors of the pylorus. He quotes a case in which he found a large pyloric tumor with marked obstruction. He performed a preliminary gastroenterostomy. When he re-opened the abdomen two weeks later, the tumor had disappeared. Evidently the tumor was not malignant, but inflammatory. I remember a similar case in which I had the same experience. However, as a rule, two-stage operations should be reserved for very exceptional and technically very complicated conditions found in the stomach. Extensive adhesions which are often disclosed on reentering the upper abdomen a short time after the primary operation, should make two-stage gastric operations the rare exception.

For many years, the two-stage operation reigned supreme in suprapubic prostatectomy. This procedure brought the mortality down to fairly low levels. In recent years the transurethral operative approach has again made the prostatic operation a one-stage procedure. However, it is yet too early to state definitely which of these two methods will survive or whether hormonal therapy may do away with suprapubic prostatectomy or transurethral resection.

In very large "pus" kidneys it is even at present accepted as a good procedure to postpone nephrectomy, until with drainage of the kidney the infection has subsided.

An extensive discussion of the two-stage procedures in colonic surgery would easily make a monograph, and would be out of place in a rather brief contribution as this is. This procedure in colonic surgery was introduced by Mieulicz thirty-five years ago. It is still used extensively, though most surgeons prefer a coecostomy in obstructive colonic lesions to the "Mieulicz Vorlagerung." Formerly two-stage operations were used in marked obstruction only. However, in recent years two and even three-stage methods are frequently employed in non-obstructive colonic lesions. For instance the Lahey procedure seems to reduce the mortality by dividing the procedure of resection of the recto-sigmoid into two steps. Whether the use of modern antiseptics, for instance, sulfanilamide, will again put the two-stage procedures in the non-obstructive lesions into the

background remains to be seen. Certainly stage procedures in colonic tumors with marked obstruction have a permanent place in surgery.

The above remarks do not exhaust the entire field of stage procedures in general surgery, and to what has already been said, mention may be made of primary drainage of the appendicular abscess and of the guillotine amputation in gangrene of the extremities. Thyroid surgery, of course, as already stated has been a favorite field for stage procedures for a long time. By these conservative methods, the mortality in Grave's disease has been lowered to below 1 per cent.

The aim of this contribution was not to discuss this subject in great detail, but mainly to draw attention to one of the many important contributions made by our senior colleague whom we try to honor by the dedication of this volume.

CHRONIC CONSTRICTIVE PERICARDITIS: MEDICAL AND SURGICAL ASPECTS

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One of the fields in which Howard Lilienthal was a pioneer is the surgery of constrictive pericarditis. In the period when surgery for this lesion was not generally advocated or advocated only by an indirect approach to the problem, he, as one of a small select company, practised the surgery of relief of the confined heart by means of excision of the constricting shell. It was our privilege to have been present and/or to have assisted him in performing such operations. A lively interest in the subject and, in particular, a desire to learn indications for operation, to develop operative technic, and to ascertain the results of operation, were inevitable sequelae. This contribution, a survey of eight operative cases studied during the past nine years, is presented as a tribute to Howard Lilienthal because of the interest he has stimulated in his followers in this field.

HISTORICAL

The clinical picture of chronic constrictive pericarditis has been considered by some to be of recent recognition, being ascribed to German authors, particularly to F. Pick (1896, Pericarditic pseudo-cirrhosis of the liver), Kussmaul (1873, Callous mediastino- pericarditis and the paradoxical pulse), Volhard and Schmieden (1923) and a number of others; but Paul D. White in a recent comprehensive review of the whole history of the subject has called attention to the fact that certain Englishmen, Norman Chevers (1842) and Wilks (1870) had previously recognized and adequately described the pathogenesis, the clinical signs and symptoms of chronic constrictive pericarditis. Even long before Chevers, however, the illustrious physiologist, Richard Lower (1669), described "callous" pericarditis and reported one clinical case with the post mortem findings. In his famous "Tractatus de Corde" (an Elzevir edition, published in Amsterdam in 1669, may be found in the New York Academy of Medicine Library) he says, under the caption of how the pericardium can alter and destroy the movement of the heart: "While the heart's capsule is stated to be of service to it on more than one account, . . . it is also often injurious to the heart in more than one way. For, just as it injures the heart by accumulation of fluid within it, so, when this is completely absent, it

approaches so close to the heart, that at length it adheres everywhere to this organ. Hence, as it is also joined to the diaphragm, it must combine and unite the heart's movement with that of the diaphragm. How great a hindrance and disadvantage this must be for both organs, I have shown above and it will be still clearer from the following story.

"The wife of a certain citizen of London, aged 30, healthy and active enough previously, . . . suffered from breathlessness on the least exertion, had a small and often an intermittent pulse, and complained almost continuously of attacks of pain and of great physical discomfort." (After three years she died and there was a necropsy.) "While examining the other organs, however, we discovered a pathological condition of the heart, to which we may rightly attribute the cause of all her troubles. The thorax was opened and the lungs were healthy enough; the pericardium, however, had become closely attached all over to the whole surface of the heart, so that it could only with difficulty be separated from it. Further, this membrane had become thick, opaque, and hard ["callosa"] instead of being thin and transparent, as it should naturally have been. Hence, as there was no space for the free movement of the heart, and no fluid for moistening its surface, it is little wonder that she complained all the time of these ills. Further, as the diaphragm is always attached to the pericardium in man, when the heart itself was also united to the pericardium, the diaphragm must of necessity have carried the heart down with it at every inspiration, and during that time must have held up and suppressed its movement" (from Dr. K. J. Franklin's English translation of pages 99 to 101 of the original London Edition of 1669).

Other names prominent in unravelling the mechanism are Cohnheim, Burwell, Claude S. Beck, Paul D. White and Churchill.

As to the surgical release of the incarcerated heart by resecting the callous pericardium as extensively as seemed safe, this was first suggested by two Frenchmen, E. Weill (1895) and Delorme (1898) and subsequently by an American surgeon, C. Beck (1901), but was first actually carried out with remarkable but only temporary success by L. Rehn (1920). Rhen resected the pericardium successfully and transplanted fascia into the defect in four children, with relief of the circulatory symptoms. Unfortunately two of the children had severe tuberculous pericarditis and so the improvement was only temporary, and the other two died of intercurrent disease twelve and eighteen months respectively after the operation. An analysis of the total literature by Claude S. Beck in 1939 revealed "that 175 patients with compression scars were operated upon by 51 surgeons";—a low figure perhaps for a condition described 270 years ago by Lower.

Chronic constrictive pericarditis may be mimicked by conditions which cause hypertension of the systemic venous circulation such as occurs in right heart failure from any cause, in superior and inferior vena cava ob-

struction, and by conditions which cause the accumulation of fluid in the body cavities, notably hepatic cirrhosis, nephrosis, polyserositis, and nutritional hypoproteinemia. The differential diagnosis between these various conditions often is not difficult and leads gradually either to elimination of other lesions or to recognition of cardiac constriction as the underlying cause of the symptom-complex. There are occasional cases, however, of progressive failure of the circulation due to coronary artery disease, myocarditis or, rarely migrating phlebitis with superior and inferior vena cava occlusion, in which the resemblance is so close and the situation so hopeless, that an exploratory operation may be necessary in order to rule out constrictive pericarditis.

Many of the cases of disturbed circulation that came under our observation during the past ten years suggested a tentative diagnosis of constrictive pericarditis. Under observation the circulatory derangement in many of the cases frequently failed to fulfill the criteria. In eight of these cases, which comprise the series presented in this paper, the diagnosis of constrictive pericarditis was made and consequently the pericardium was explored. In addition, there were two cases in which the diagnosis was made and not confirmed at operation. Reference also should be made to a patient suffering from circulatory failure in whom the diagnosis of constrictive pericarditis was entertained. Operation was planned but death intervened and the necropsy revealed only diffuse myocardial disease.

Case 1. Idiopathic Constrictive Pericarditis of Six Months' Duration. Syndrome Matured under Observation with Development of Ascites. Initial Pleural Exudates Followed by Transudates which Required Repeated Thoracenteses. Pericardiectomy Followed by Progressive Circulatory Improvement and Economic Restitution. Patient Well Eight and a half Years after Operation.

History (Adm. 375884). M. K., a 39 year old tinsmith, was admitted July 30, 1931. Six months before admission he began to have dyspnea on effort; this increased progressively and was associated with substernal pressure at first on exertion, and later even while at rest. He passed little urine. His temperature was 102°F.

Examination. Cyanosis of the fingers and lips was present. There was evidence of fluid at both bases. The heart sounds were faint; the heart rate was 112 beats per minute. The liver was enlarged to four finger-breadths below the free costal margin. There were no ascites. Admission diagnosis: Cardiac failure (right and left) secondary to hypertension or rheumatic fever.

Laboratory Data. On admission: slight leucocytosis (16,900) with 68 per cent polynuclear cells. Erythrocyte sedimentation rate was over two hours. There were thirteen thoracenteses, the fluid of the two first indicating an exudate, the subsequent ones transudates. The abdominal fluid from the ascites which developed after admission showed a specific gravity of 1010 and contained 90 per cent lymphocytes. The guinea pig inoculation and Lowenstein cultures of ascitic and pleural fluids were negative for tuberculosis. An electrocardiogram showed tendency to

left axis deviation, QRS of low voltage in all leads; T_1 and T_2 inverted, T_3 low. The antecubital venous pressure was 16 to 20.5 cm.

Course. During his stay dyspnea, pulsus paradoxus and gallop rhythm appeared. In spite of the administration of digitalis, salyrgan and repeated thoracentesis, pleural fluid returned and ascites and ankle edema appeared. In view of this the diagnosis of constrictive pericarditis was suggested.

Operation (November 20, 1931). A flap incision was made and the pericardium exposed without the removal of a rib. The pericardium, which was whitish and immobile, was incised over the presumed site of the left ventricle. The pulsating heart appeared in the pericardial gap. More and more of the heart gradually presented in the cleft that was made. Excision of the membrane was begun by first freeing the left ventricle completely. After the heart was completely released over its left aspect, a similar dissection over the right ventricle was carried out. The heart was pulsating with considerable force and came up into the operative field. There was, however, an additional smooth whitish layer of tissue clinging to the heart which required removal in order to release the heart completely. This was excised cautiously; it consisted of a uniform layer, 0.3 to 0.6 cm. in thickness. The real release of the heart occurred as this layer was removed. The surface of the underlying heart was greyish in color. The incision and subsequent excision of the constricting pericardium over the right side of the heart to the venae cavae and including the apex was carried out. Although the right ventricle and venae cavae were not identified, the impression gained was that a thorough release of the heart from the membrane which confined it had been obtained. The blood pressure before operation was 98 systolic and 80 diastolic, but rose to 116 systolic and 90 diastolic when the heart was released.

The surgeon's comments were as follows. The two characteristic layers of the pericardium with a softer tissue between (resembling a "bread and jam" sandwich) did not constitute the entire pathologic lesion. There was in addition a confining layer around the heart, presumably epicardium. A definite rise of blood pressure occurred only after the layer of altered epicardium was removed, with complete release of the heart. It was impossible to distinguish the great vessels or indeed the four chambers of the heart during the operation. The flap incision, without removal of a rib, gave an adequate exposure of the heart.

Course. The venous pressure remained elevated (14.5 to 16 cm.) immediately after the operation, but gradually fell to 10 cm. The hepatic enlargement and peripheral edema gradually subsided. The patient was discharged in January 1931.

On re-admission in February 1933 there was general improvement. Blood pressure was 132 systolic and 90 diastolic. Circulation time with the saccharin method was 20.5 seconds and 15.5 seconds. Venous pressure was 5 cm. In addition there was some electrocardiographic evidence of improvement. On re-admission in January 1935, there was slight diminution of cardiac reserve. Venous pressure was normal (4 cm.) with a rise of 3.5 cm. on right upper quadrant compression. He returned to his occupation as a tinsmith and was well as late as April 1940. The "swallowing sign," however, remained positive.[1]

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[1] The swallowing sign (Rabin) has been of value in the diagnosis of chronic adhesive mediastinitis. Normally, on fluoroscopic examination swallowing does not cause an elevation of the mediastinal structures. The sign is positive when, during deglutition, there is an elevation of the aortic arch and the heart itself.

See Rabin, Coleman B.: "Diagnostic Roentgenology" Edited by Ross Golden, Thomas Nelson and Sons, New York, p. 186, 1938.

Comment. This was an early case of constrictive pericarditis when first seen with evidence of an active subacute inflammatory process, indicated by the fever and the exudate in the pleural cavities. The later appearance of the ascites and the character of the ascitic fluid indicated that this resulted from the constrictive pericarditis rather than from the polyserositis. The etiology of the polyserositis was obscure. Surgical release of the heart was followed by marked improvement, indicating that the congestive, rather than the inflammatory, factor was of paramount importance in the syndrome. The persistence of the positive swallowing sign, despite clinical improvement, suggests that the mediastinitis which accompanied the pericarditis played a relatively unimportant role in the genesis of the symptoms.

Case 2. Chronic Polyserositis Associated with Apical Tuberculosis. Typical Constrictive Pericarditis Operated Upon during the Sixth Hospital Admission. Accidental Perforation of Right Ventricle during Dissection of Pericardium. Death Three Days Postoperatively from Heart Failure and Shock.

History (Adm. 338874). S. K., a 39 year old male, was admitted on November 3, 1931 with a history of three previous hospital admissions. The first admission in 1925 was for recurrent epigastric and abdominal pains, with fever. The sputum was negative for tubercle bacilli. The discharge diagnosis after an abdominal operation was: 1) subacute cholecystitis; 2) chronic appendicitis; 3) inactive pulmonary tuberculosis, and 4) chronic parenchymatous degeneration of the liver. He continued to run a fever. He was admitted for the second time on January 17, 1926 because of abdominal symptoms. On exploratory laparotomy, a large, smooth liver was found with some ascites. Liver biopsy revealed a slight hepatitis. He was admitted for the third time in September 1929 for dyspnea, hydrothorax, edema of the legs, enlarged liver, swelling of the abdomen, and increased prominence of the veins on the abdomen, arms and neck. This time the discharge diagnosis was chronic mediastinitis with venous obstruction.

Examination. The patient had a waxy color and cyanosed lips. The peripheral veins were prominent. There was bilateral hydrothorax, ascites and edema. No cardiac impulse could be detected. No Broadbent's sign was present. Blood pressure was 86 systolic and 70 diastolic.

Laboratory Data. Venous pressure was 25 cm. Right chest was tapped twice and fluid was removed with a specific gravity of 1013, 785 cells per cu. mm. of which 80 per cent were monocytes. Guinea pig inoculation with the pleural fluid was positive for tuberculosis. An electrocardiogram revealed low voltage of all the deflections, suggesting marked impairment of myocardial function. Diagnosis of polyserositis with constrictive myocarditis was made, but the patient refused pericardiectomy and was discharged.

Course. The patient was re-admitted on March 4, 1932 with an increase of his previous symptoms for which he received medical treatment.

He was admitted for the sixth time on May 7, 1932, and gave consent for a pericardiectomy. Fluoroscopy confirmed the presence of fixation of the heart. An electrocardiogram taken in different positions failed to show any appreciable changes in the ventricular complexes on change of posture.

Operation (May 13, 1932). After a left-sided flap was made, sections of the third to the sixth costal cartilages were excised. A segment of the pericardium was removed over the left ventricle, and the heart protruded into the defect that had been made. While further dissection was being carried out presumably, but as it turned out not actually, over the left ventricle, bleeding occurred which could not be controlled by suture because the latter tore through. The bleeding was controlled by pinching the heart muscle, and subsequently by gauze packing. No further effort was made at excision and the wound was closed. After the operation no further hemorrhage occurred, but there was a left-sided pneumothorax. Venous pressure was over 28.5 cm. In spite of treatment, pulmonary edema set in and the patient died three days after the operation apparently from heart failure and shock.

Necropsy Findings. Perforation with suture of the right ventricle. Chronic serositis involving pleura, pericardium and hepatic ligaments. Cardiac fibrosis of the liver. Chronic passive congestion of the viscera. Marked hypertrophy and dilatation of both auricles. Moderate hypertrophy of both ventricles. Fatty degeneration of the myocardium. Dilatation of hepatic veins and venae cavae. Anasarca, hydrothorax and ascites. Healed apical tuberculosis. The heart was completely encased in a dense white membrane about 1 cm. thick. There was an excavation of the fibrous membranes over the right ventricle, with a perforation of the myocardium through which a probe could be passed. There were no constricting bands about the caval vessels. The pericardium was unusually adherent so that at necropsy no cleavage plane could be established.

Comment. This case illustrates the natural history of tuberculous polyserositis, which terminated in constrictive pericarditis which was at first erroneously diagnosed as intra-abdominal disease. It is to be regretted that the pericardiectomy was performed so late that the old thickened pericardium presented no plane of cleavage, also that the prolonged incarceration of the heart had caused secondary degenerative changes in the myocardium, and finally that the rotation of the heart was of such a degree that only the right heart presented when the precordial space was exposed which led to the accidental rupture of the myocardium of the right ventricle. The case indicates that one cannot in advance predict the type of pathologic change, nor the degree of operability of the presenting pathologic syndrome.

Case 3. Acute Episode (Polyserositis?) Four Years Before Admission. Anasarca Due to Constrictive Pericarditis Superimposed on Chronic Rheumatic Cardiovalvular Disease. Brauer Cardiolysis and a Partial Pericardiectomy Afforded Transitory Relief. Second Pericardiectomy Followed by Relief after Months and Ultimate Economic Restitution. Terminal Adenocarcinoma of Rectum.

History (Adm. 332334). D. R., a 37 year old paper-hanger, was admitted on November 16, 1931 complaining of dyspnea. He had a history of heart trouble since the age of 15 years. In 1917 he had a febrile illness lasting nine weeks with fluid in the chest and on the heart. In 1928 he suffered from edema of legs, abdomen and scrotum. In 1929 a Brauer cardiolysis was performed at another hospital, with the removal of 3 or 4 ribs. In 1930 he was re-operated upon and a tremendously thick-

ened and completely adherent pericardium was found. About one half of the pericardium was removed and the visceral pericardium was found to be as thick as "shoe leather." He showed some improvement.

Examination. On admission he presented cyanosis, distension of cervical veins, hydrothorax, enlargement of the heart, signs of mitral stenosis and insufficiency, auricular fibrillation, enlargement of the liver, ascites and anasarca. The admission diagnosis was: 1) Pick's syndrome on the basis of a rheumatic polyserositis and 2) chronic rheumatic valvular disease with mitral stenosis and insufficiency and auricular fibrillation. Venous pressure was 20 cm. An electrocardiogram showed auricular fibrillation, right axis deviation, low voltage of R and T waves in all leads.

Operation (December 4, 1931). A large left-sided flap was made. The third to sixth left costal cartilages and a section of sternum were removed, exposing the pericardium through which the heart could be seen pulsating slightly. Laterally this layer was continuous with a much thicker layer. This layer was incised over the site of the left ventricle and the heart released until it protruded through the opening. The inner and outer layers together were 1.5 cm. thick; they were removed over both ventricles. The right auricle was next released, revealing a fibrillating and edematous surface. The superior vena cava was not dissected out. After bluntly dissecting the apex of the heart, the region of the inferior cavae was palpated, but no constricting bands were felt. The skin flap was sutured.

Postoperative Course. The patient recovered from the operation, but the fluid continued to accumulate in various parts of the body in spite of apparently good treatment. Only months later did the patient confess that he had bribed an attendant to secure unlimited quantities of fluid. After many weeks of unsuccessful attempts at treatment, the patient was admitted to Montefiore Hospital where he improved remarkably, so that by December 1932 he was partially restored to economic usefulness. He was readmitted to the hospital on February 17, 1933. The venous pressure was 14.5 cm., with a rise to 19.5 cm. on right upper quadrant pressure. He could endure a moderate amount of exertion without dyspnea. Proctoscopic examination, however, unfortunately revealed the presence of a large polypoid adenocarcinoma of the rectum, from which he died several months later.

Comment. This case is one of constrictive pericarditis probably following a rheumatic polyserositis. Rheumatic fever is an exceptional cause of constrictive pericarditis. The enlargement of the heart was probably due to his rheumatic valvular disease. This illustrates the point that the presence of a large heart does not necessarily exclude constrictive pericarditis, especially when some other cause for the enlargement is found. The case also emphasizes the ineffectiveness of the Brauer cardiolysis alone, and the good result which may be achieved by repeated pericardiectomy even in the presence of severe rheumatic heart disease. The delay in getting the satisfactory result after the operation at the hospital may be attributed to two factors: 1) cardiac insufficiency on the basis of prolonged valvular disease and the myocardial atrophy of prolonged incarceration, and 2) unrestricted fluid intake.

Case 4. Calcified Chronic Constrictive Pericarditis of Insiduous Onset Three Years Duration. Twenty Paracenteses Before Operation. Masked Anatomic Landmarks due to Adhesive and Calcific Processes Leading to

Accidental Initial Dissection of Pericardium Over Right Ventricle (Assumed to be the Left Ventricle) and to a Rupture of the Right Ventricle. Death Seven Days Post-operatively Due to Bronchopneumonia, Heart Failure and Shock.

History (Adm. 387881). R. S., a 49 year old woman, was admitted on December 16, 1935 without a history of tuberculosis or rheumatic fever. Edema of the ankles had occurred twenty-two years before. Three years before admission she had begun to complain of dyspnea, night sweats and cyanosis, followed by subcutaneous edema. In 1933 her hemoglobin was 40 per cent and she received a transfusion. Subsequently she developed ascites, which recurred and required twenty abdominal paracenteses.

Examination. She was poorly developed and undernourished. The cervical veins were distended. There was systolic retraction of the anterior left lower ribs. The heart was slightly enlarged; auricular fibrillation was present. The liver and spleen were enlarged. Admission diagnosis: Concretio cordis with Pick's syndrome and auricular fibrillation.

Laboratory Data. Blood examination revealed anemia with eosinophilia. Blood pressure was 122 systolic and 73 diastolic. The venous pressure was 18.5 cm. with a rise on right upper abdominal compression to 29.5 cm. The circulation time with ether ("arm to lung" time) was 8 seconds, with saccharin ("arm to tongue" time) was 18 seconds. X-ray examination of the chest showed: calcification of the pericardium. The right oblique view showed a band of calcification extending across the anterior surface of the left ventricle. An electrocardiogram showed auricular fibrillation, QRS of moderately low voltage; T waves iso-electric in all leads.

Course. Repeated mercupurin injections, paracenteses, limitation of fluids and digitalization failed to change the clinical picture. So, in spite of the calcification, it was decided to attempt pericardiectomy.

Operation (January 3, 1936). After the usual flap incision, the second to fifth costal cartilages and adjacent portions of sternum were removed. The pericardium with a shell of calcium was incised and then dissected downward and upward. This was done presumably over the left ventricle, but there was a sudden hemorrhage which was controlled by the finger and tampon. A strip of the calcified plaque about 2 by 3 inches was removed, but no plane of cleavage could be found and release of the heart could therefore not be carried out. A strip of gauze was carried out of the lower end of the wound and the remainder closed in layers.

Postoperative Course. On the second postoperative day the venous pressure was 27 cm. and slight abdominal pressure caused a further rise. The patient became weaker, and finally died, seven days after operation, of bronchopneumonia, heart failure and shock.

Necropsy Findings. The right ventricle was perforated and a polyserositis was present characterized by a total adhesive pericarditis with calcification, bilateral adhesive pleurisy, chronic peri-hepatitis and peri-splenitis, chronic peritoneal thickening. In addition there was a fibrosis of the liver (pseudo-cirrhosis), phlebosclerosis of the venae cavae and hepatic veins, and a bronchopneumonia. The entire heart was surrounded by adherent pericardium about 3 mm. thick, and included a calcific ring 1 to 3 mm. thick and about 4 cm. wide, except where a portion had been removed at operation. At the auriculo-ventricular sulcus and at the basilar portions of both ventricles, where the pericardium was calcified, it was not possible to detach the pericardium without tearing the musculature. The heart was small; the right and left auricles were slightly dilated. The myocardium of both ventricles was of a brownish-red color and firm texture. An oblique perforation of the right ventricle,

1 cm. long, was present. In certain places the dense connective tissue extended into the myocardium in the form of a broad wedge where there was also calcium deposition.

Comment. The etiology of the polyserositis in this case is obscure. The onset was anywhere from three to twenty-two years before with the gradual development of the classical picture of venous hypertension, ascites and a small heart. When the patient first came under our observation, she already had a calcified pericardium. This made diagnosis a simple matter, but the prognosis was poor since calcification renders the surgical release of an incarcerated heart very difficult, and is usually associated with a brown atrophy of the myocardium. The rupture of the right ventricle was probably not due to direct trauma, but resulted from the passive abnormal distension of a freed, unsupported segment of atrophic degenerated right ventricle combating an abnormally high intrapulmonary arterial pressure.

Case 5. Constrictive Pericarditis of One and a half Years' Duration. Syndrome of Venous Hypertension, Small Heart and Ascites. Partial Pericardiectomy Ineffective. Second Operation via Transthoracic Approach. Adequate Release of the Heart. Freedom from Symptoms and Fluid Reaccumulation. Well Four Years after Operation.

History (Adm. 388710). T. M., a 38 year old English laborer was admitted to the hospital in January 1936 because of ascites of one and a half years' duration. In his early youth he had had intermittent severe pain in the legs, particularly at night. He had been on active Army service from 1914 to 1917 and in 1917 he had had pleurisy. In June 1934 he was admitted to a hospital because of dyspnea, orthopnea, weakness, and swelling of the ankles of one years' duration. The diagnosis was congestive heart failure. Fluid was present in both chests and in the abdomen. His right chest was tapped and salyrgan injections given. He was discharged unimproved, after a prolonged stay. In January 1935, he was admitted to another hospital because of recurrent ascites. A laparotomy was performed. Because of the firmness of the liver with marked thickening of the capsule, the diagnosis of cirrhosis was made and an omentopexy was performed. Ascites continued despite salyrgan injections. There were readmissions for thoracic and abdominal paracenteses during the remainder of 1935.

The patient was admitted to still another hospital in October 1935, where a diagnosis of adhesive pericarditis was made.

Examination. On admission to The Mount Sinai Hospital there were noted moderate emaciation, slight cyanosis of the lips, and orthopnea. The veins in the neck were distended, and showed inspiratory filling. There were signs of fluid in the right chest. There were no heart murmurs; A2 equalled P2. Heart sounds were of fair quality. There was no Broadbent sign. The blood pressure was 105 systolic and 85 diastolic. There was no paradoxical pulse. The abdomen was distended with fluid. The liver was palpable three finger-breaths below the costal margin.

Laboratory Data. The venous pressure was 23 cm. and rose to 36 cm. on right upper abdominal compression. The ether time ("arm to lung" time) was 12.5 seconds. The saccharin time ("arm to tongue" time) was 26 seconds. The venous

pressure measurement eleven days later was 24 cm. rising to 36 cm. on right upper abdominal compression. Inspiration and expiration produced a .5 cm. rise and fall respectively in venous pressure. The abdomen was tapped twice with the removal of 6.5 and 5.5 quarts of fluid. The specific gravity of the fluid was 1.012. The count was 40 cells per cu. mm., of which 80 per cent were mononuclears and 20 per cent polynuclears.

X-ray examination of the chest on admission showed fluid in the lower third of the right pleural cavity with thickening of the pleura of both lungs, particularly the right; the right leaf of the diaphragm was somewhat elevated. The heart was triangular in appearance, its left border sharp and straight, probably because of the pleuropericardial adhesions. Subsequent X-ray examinations of the chest showed very little change other than reaccumulation and absorption of the pleural transudate.

An electrocardiogram showed only slight shift in the axis of the heart when the record was taken in the right lateral position, and no shift when the patient was in the left lateral position; right ventricular preponderance was present, T_1 was iso-electric, T_2 and T_3 inverted. There were no essential changes in electrocardiograms taken during the patient's stay.

Course. The history, the clinical course before admission, the physical signs notably ascites, hydrothorax, and distended systemic veins with their inspiratory filling, the circulatory measurements (particularly the persistent elevation of the venous pressure after long bed rest and therapy), and the X-ray film of a small heart, offered convincing evidence that the patient had a constrictive pericarditis. During a prolonged period of hospital study, there was persistent invalidism due to reaccumulation of pleural and peritoneal fluid, despite abdominal and thoracic paracenteses, limitation of fluids, digitalis and mercurial diuretics. Pericardiectomy, therefore, was decided upon.

Operation (February 4, 1936). The pericardium was approached through an essentially parasternal extrapleural approach, although the right pleura was entered. It was almost immobile. Avascular pericardium one-quarter of an inch thick was traversed in order to expose the heart. The epicardium was gray. The diseased pericardium was freely removed, most liberally over the assumed site of the left ventricle after a plane of cleavage was found. After the dissection released the right ventricle (and auricle?), the heart escaped from the confining membrane, bulged far forward, and its contractions became vigorous. The blood pressure rose and the rise was maintained.

Postoperative Course. There was a low grade infection of the wound, which cleared up slowly. The patient's general condition at first improved markedly. The elevated blood pressure was maintained (around 116 systolic and 76 diastolic), but the venous pressure did not drop to normal (range between 15 and 20 cm.). After a short time there was recurrence of intra-abdominal and pleural fluid. Medical therapy was not effective and a second operation was decided upon with the object of releasing the left heart more freely.

Operation (April 17, 1936). Through a deliberately made left transpleural approach the left ventricle could be widely exposed. There was no recurrence in the region of the former excision of pericardium. The partial and transient result of that operation was due to: 1) incomplete removal, and 2) too limited removal of the scar tissue over the left heart. At this operation the thickened pericardium was widely removed over the left heart; the heart appeared completely released when the dissection to the diaphragm had been completed.

Postoperative Course. There was more shock than after the first operation and a mild infection of the wound. At first the venous pressure remained somewhat elevated (16 cm.). Subsequently progressive improvement set in.

Fluid in the peritoneum or pleura did not reaccumulate at any time. The liver had receded, and was no longer palpable. The venous pressure two years after operation was 8 cm. The veins in the neck were not distended. The patient was essentially asymptomatic and was almost completely restored to normal health.

Comment. This case illustrates strikingly the difference between a partial and transient result of operation and a good result. The latter was achieved by a wide liberation of the left heart, in contrast to the indifferent result following release of much of the right, and relatively little of the left heart. A deliberately performed left transpleural approach performed for the first time in this case made possible the extensive decortication of the left heart.

Case 6. Constrictive Pericarditis with Calcification of Eight Years' Duration. Venous Hypertension, Small Heart, Ascites. Partial Pericardiectomy with Incomplete Removal of Calcific Plaque. No Escape of Heart Through Pericardial Hiatus. Pronounced Improvement. Two Year Result.

History (Adm. 397259). P. S. M., a 20 year old Italian girl, was admitted to the hospital in August 1936. In childhood she had three attacks of polyarthritis. She had been under observation and treatment in the Out-Patient Department since the age of twelve years. The chief complaints had been shortness of breath, palpitation, recurrent ascites, and edema of the legs. Digitalis had been administered throughout this long period, particularly during phases of bed rest. Hospital admission had been repeatedly refused up to 1936. Repeated roentgenological examinations of the chest always revealed thickening of the right pleura, with occasional effusions.

Examination. The patient was well nourished, lying comfortably in bed. The cervical veins were prominent and distended. The trachea was deviated to the right. There were signs of fluid in the right chest. The heart sounds were of good quality; A2 loud and snapping; P2 louder than A2; soft systolic murmur at base; moderate pulsus paradoxus. Blood pressure was 130 systolic and 90 diastolic. The abdomen contained considerable fluid. The liver was palpable several inches below the costal margin. There was pitting edema of the lower extremities and sacral region.

Laboratory Data. The hemoglobin was 60 per cent. The electrocardiogram showed a tendency to right ventricular preponderance. The venous pressure was 21.5 cm. in the right arm, 20 cm. in the left arm. After rest in bed and a good response to mercupurin the venous pressure was still 22 cm. X-ray examinations of the chest revealed a small, loculated, right-sided, pleural effusion, and marked thickening of the right pleura.

Course. The chronic adhesive pleuritis, the markedly elevated venous pressure, the enlarged liver, ascites, and peripheral edema, all in the presence of minima-subjective complaints, suggested the diagnosis of Pick's disease. There was excellent response to 2 cc. of mercupurin, most of the ascites and peripheral edema disappearing. There was, however, no change in venous pressure.

The patient was re-admitted two years later. In the interval digitalis had been administered. Symptoms were moderate dyspnea on exertion, fatiguability, intermittent edema of the legs. One month before admission marked abdominal distension developed with a diminished urinary output.

Examination. The patient was poorly nourished. The veins of the neck were cord-like. Fluid was present in both chests. The heart was not enlarged; a soft systolic murmur was heard at the apex; no Broadbent sign was present. The abdomen was unusually protuberant and contained much fluid. The liver was considerably enlarged. There was pitting edema of legs, thighs and over the sacrum.

Laboratory Data. The blood pressure was 102 systolic and 72 diastolic. The initial venous pressure was 28 cm. with a rise on right upper abdominal compression to 45 cm. At that time the patient weighed 146 pounds. After mercupurin diuresis and abdominal paracentesis with the removal of a large amount of fluid, with a specific gravity of 1.018, the patient lost 45 pounds. The subsequent venous pressure was 14 cm. with a rise on right upper quadrant compression to 24 cm. showing a marked lowering of the initial venous pressure, but a response on abdominal compression which was relatively proportionate to the height of the initial venous pressure. The X-ray examination of the chest revealed displacement of the heart to the right. Linear dense streaks within the cardiac shadow suggested areas of calcification.

Because of the presence of calcification, the clinical picture was attributed to constrictive pericarditis despite atypical features.

Operation (June 3, 1938). A left-sided transpleural approach was employed, and the left lateral aspect of the heart was exposed. Although the pericardium was thickened, and intrapericardial adhesions were found, the lesion was not pronounced and the heart did not bulge into the hiatus left by partial excision of the pericardium. The excision was, therefore, carried over to the right side and here a plaque of calcification was encountered. Much of this was excised, but there still was no great protrusion of the heart into the hiatus. It was thought that at some future time further operative excision of the plaque over the right heart might permit of additional improvement if, in fact, some improvement followed the procedure which had been carried out.

Postoperative Course. There was no obvious immediate improvement, although ascites following paracenteses recurred more slowly. The venous pressure remained elevated.

Ten months after operation, considerable improvement was noted, the patient having required but one abdominal tap since leaving the hospital. She was still receiving mercupurin and there was moderate ascites at the time of examination.

Two years after operation, the general condition was excellent and digitalis had not been administered since operation. Liver and spleen remained enlarged. There was slight ascites and some ankle edema. The only symptom was slight dyspnea on active exercise. Ammonium chloride and mercupurin were still being administered. Elevated venous pressure persisted. The patient was doing part-time work.

Comment. The improvement which took place in this case was unexpected, and the view that a more extensive decortication would be required could not be maintained. The explanation for the partially successful result is not obvious, since there appeared to be no great interference with heart action by the adherent pericardium. The latter was much less thick than that seen in classical cases.

Case 7. Constrictive Pericarditis of Nine Years' Duration. Diagnosed Cirrhosis of Liver. One Hundred Fifty-two Abdominal Paracenteses. First Operation Ineffective. Second Partial Pericardiectomy, Yielding Remarkable Improvement.

History (Adm. 489871). J. V., a 41 year old Italian woman with a nine year history of frequently recurring ascites for which 150 abdominal paracenteses had been performed, was admitted on September 20, 1938. Her sole complaint was recurrent ascites. In 1931 the patient had an exploratory operation at another hospital where the liver was found to be markedly enlarged, irregular and scarred. On the diagnosis of Laennec's cirrhosis additional operations were performed without improvement. In 1937 edema of the face and lower extremities developed. Radiotherapy was administered to the abdomen at a third hospital between January and July 1938 on the assumption of malignancy. Subsequently (July 1938), a sapheno-peritoneostomy was performed without result.

Examination. The patient appeared chronically ill. The heart was not enlarged; there were no murmurs; P2 was louder than A2. The liver was firm, sharp-edged, somewhat irregular and palpable about three inches below the costal margin. There was a large amount of fluid in the abdomen. There was no edema.

Laboratory Data. Blood pressure was 110 systolic and 80 diastolic. The hemoglobin was 70 per cent. Abdominal paracentesis was performed with the removal of 11,000 cc. of straw-colored fluid; specific gravity, 1008; no tumor cells. Pneumoperitoneum: Large liver and large spleen.

Circulatory Measurements. High initial venous pressure (18.5 cm.) and marked rise during right upper quadrant compression, definitely indicative of right ventricular failure. Subsequently, abdominal paracentesis was performed with the removal of 5,000 cc. of fluid. The venous pressure with the abdomen empty was 9 cm. Compression of the right upper abdominal quadrant or left lower quadrant caused a rise of 9.5 cm. On the following two days the venous pressure in the antecubital vein was only 8 cm. and 7 cm. respectively, but each time the abdominal compression caused a rise of 12 and 12.5 cm. The lowering of the initial venous pressure threw doubt on the diagnosis of constrictive pericarditis. It was argued, however, that the lowering of the initial venous pressure was not as significant as the effect of right upper quadrant compression and that the presence or absence of ascites determined the level of the initial venous pressure in this patient. The venous pressure rose progressively to 17 cm. upon reaccumulation of peritoneal fluid.

A roentgenogram of the chest showed elevation of both leaves of the diaphragm. The heart was markedly widened at the base and its borders were irregular, as in cases of extensive pericardial adhesions. With change in position of the patient there was no change in the position of the heart. Pulsations over the lower left contour of the heart were diminished. There was relatively little change in the density of the pulsations as observed kymographically. An electrocardiogram showed regular sinus rhythm, tendency to left ventricular preponderance; P waves wide and notched; R-T transition depressed in lead 1, T_2 flat, T_3 inverted, T_4 semi-inverted. An electrocardiogram taken in left and right recumbent positions showed only very slight changes in electrical axis.

Course. During the period of study the patient received enormous doses of digitalis, mercupurin, ammonium chloride, and vitamin B. Despite this therapy, administered on the possibility of other lesions than constrictive pericarditis as the cause of ascites, the patient continued to gain in weight. Thus, despite atypical features, the foregoing observations, the presence of venous hypertension (during ascites), the absence of significant enlargement of the heart, the roentgenographic features, and the well-being of the patient over a long period of time, justified the diagnosis of constrictive pericarditis. It was realized, however, that if the diagnosis was correct, the case was unique. An exploratory operation appeared warranted since there had been no relief from ascites over a very long period. Because of the atypical venous pressures and the prominence of the ascites, a block of the inferior vena cava was postulated.

Operation (December 6, 1938). Accordingly, a right-sided approach was made

to the right lateral aspect of the heart. The pericardium was found to be greatly thickened and immobile. The surface of the heart was widely freed, especially in the region of the inferior venae cavae. However, the heart did not escape into the gap in the dramatic manner ordinarily observed, but rather it appeared in the gap, protruding progressively during the remainder of the operation. The release of the heart was completed by excision of the thickened pericardium down to the diaphragm, upwards to expose the region of the right auricle, and mesially well across the midline. With the patient tilted over towards the left side, the freed inferior venae cavae could be seen.

Postoperative Course. This was complicated by a hemorrhagic pleural effusion, treated by thoracentesis. There was slow reaccumulation of ascites. Following the operation the venous pressure was 6 cm., but on right upper abdominal compression there was still a rise to 16 cm. Three weeks after operation the venous pressure was 7.5 cm., but when the abdomen was compressed it rose to 23 cm. Because of these venous pressure measurements and the reaccumulating ascites, persistence of a constricting factor was diagnosed.

Course. The patient was re-admitted on May 13, 1939. Since discharge, ascites had reaccumulated as before and repeated abdominal paracenteses had been performed, the last one being carried out three weeks before the operation. The circulatory measurements now were about the same as during the original admission. With confirmation of the impression that no result had been achieved by operation, a more radical excision was decided upon.

Second Operation (May 19, 1939). A left-sided transpleural approach was made. The excision of the thickened and adherent pericardium over the left heart was widely carried out. Toward the right side of the heart the parietal pericardium was especially thickened with plaque-like formation.

Postoperative Course. After four weeks, there was considerable ascites and a paracentesis was done. Following this the patient was discharged to be followed up in the Out-Patient Department. There was some reaccumulation of ascites, but this slowly subsided after a period of several months.

During her entire illness the patient had had 176 abdominal paracenteses. When she was examined in 1940, there was no definite evidence of ascites. The veins in the neck were not visibly distended and no abdominal paracenteses had been performed since discharge from the hospital one year before.

Comment. This dramatic case, in which the excellent result was unexpected, is without parallel in the history of constrictive pericarditis. More than any other case in this series it demonstrated the value of accurate venous pressure measurements in the diagnosis.

Case 8. Constrictive Pericarditis of Six Months' Duration. Syndrome of Venous Hypertension, Small Heart and Ascites. Partial Pericardiectomy. Elevated Venous Pressure Four Weeks after Operation. Disappearance of Ascites.

History (Adm. 458359). N. B., a 23 year old clerk, entered the hospital in June 1940. Two and a half years previously a physical examination revealed no abnormalities. Five months before admission increase in the size of the abdomen was noted. Two months later a physician diagnosed fluid in the abdomen. An hydrocele developed. One of us (W. M. H.) then saw the patient and diagnosed constrictive pericarditis on the basis of venous hypertension, ascites and a small heart.

Examination. The patient did not appear ill. There was no dyspnea nor orthop-

nea. The cervical veins were distended, filling from below in the sitting position. A marked hepato-jugular reflex was present. The lower chest bulged, due to abdominal distension by a large amount of fluid. The heart sounds were of good quality, A2 was louder than P2. The blood pressure was 126 systolic and 96 diastolic. A non-tender liver was palpated three inches below the costal margin. A small left-sided hydrocele was present. There was no edema.

Laboratory Data. The venous pressure was elevated as had already been noted (W. M. H.) before admission. Studies which cannot be detailed here proved that, according to circulatory dynamics, the existence of right heart failure was definitely established. The electrocardiogram revealed bradycardia and a tendency to right axis deviation, low T waves and notched P waves, Electrocardiograms taken in the left lateral position caused a more marked right axis deviation; in the right lateral position the right axis deviation disappeared. The roentgenogram of the chest revealed no abnormality in the lungs or pleura. The diaphragm appeared slightly elevated, the cardiac silhouette was of small size. On fluoroscopic examination there was no evidence of enlargement of the left auricle. The roentgenkymogram showed a distinct diminution in the pulsations of the left heart border. Fairly good pulsations were noted over the remainder of the cardiac shadow. On contrast visualization of the cardiac chambers with diodrast, both ventricles showed considerable dilatation.

Course. Shortly after admission the patient's weight was 143 pounds. Treatment with mercupurin, digitalis, and ammonium chloride, and restriction of fluids caused a progressive drop in weight to 126 lbs. Because the diagnosis appeared established and there was no other known curative therapy, operation was decided upon.

Operation (July 19, 1940). The heart was approached from the left side through a liberal transthoracic incision. An immobile whitish pericardium of no great thickness was encountered. Extensive piecemeal removal of freed flaps of thickened pericardium was carried out. The heart bulged and pulsated vigorously. A thin grayish-white layer which was wrinkled on contraction was still visible over the left heart. After freeing the left heart, the pericardium was dissected away from the right heart. The large vessels at the base of the heart were not visualized.

Postoperative Course. There was a collection of bloody fluid in the left pleural cavity which was removed by Potain aspiration. Otherwise the postoperative course was uneventful. Elevated venous pressure has persisted since operation. However, ascites has not recurred.

Comment. This case illustrates the well-known fallibility of the electrocardiographic method of determining the mediastinal fixation of the heart, an aid in the diagnosis of constrictive pericarditis. Evidently fixation of the heart is not necessarily an accompaniment of constrictive pericarditis. Again this case demonstrates that symptomatic cure (disappearance of ascites) can be accomplished by pericardiectomy even though the venous pressure curve may still show the characteristic curve of right heart failure. The period of time after operation is too short to refer to any result other than an interval one.

MEDICAL ASPECTS

Paul D. White's review of the history and clinical features of Pick's disease and Beck's experimental and surgical work on constrictive peri-

carditis have helped considerably in clarifying the situation in respect to chronic constrictive pericarditis. The ordinary localized and generalized forms of adhesive pericarditis, as seen on the post-mortem table following myocardial infarction, acute rheumatic fever or pneumonia, cause no alteration in the dynamics of the circulation such as is observed in constrictive pericarditis. The cases presented in the foregoing protocols deal with an *extrinsic* form of heart disease in which scars representing a thickened contracted, at times calcified, pericardium, incarcerate and compress the heart interfering with its diastolic expansion, less markedly with its systolic contraction, causing thereby extreme venous stasis. This encasing membrane arises either idiopathically, or is associated with tuberculosis or pneumonia, or exceptionally as an aftermath of rheumatic fever. In our series of eight cases, the etiology of five cases was obscure (the so-called idiopathic type), one was tuberculous in origin, and in the other two there was a clinical history of rheumatic fever. Although several of our cases presented definite evidence of pre-existing polyserositis, the transition from the inflammatory to the compression stage was observed in only one instance (Case I) in which the picture evolved under our observation. It is paradoxical that the terminal phase with its circulatory sequelae really represents the healing or healed stage of a previous diffuse inflammatory process.

The symptoms of chronic constrictive pericarditis are primarily due to constriction and *not* to the fixation of the heart to surrounding structures. The diagnosis may be made on the history and at times even on inspection alone. The triad of Beck which offers a valuable working combination for the recognition of this disease, consists of 1) a small quiet heart; 2) venous hypertension; and 3) ascites and an enlarged liver. Additional physical and laboratory findings are those that are generally observed in circulatory failure except that dyspnea and orthopnea are not prominent features. With the exception of the size of the heart, which may even be smaller than normal, and the roentgen and kymographic findings of diminished cardiac excursion, mediastinal fixation, esophageal distortion, Rabin's swallowing sign and possible pericardial calcification, the signs and symptoms resemble closely those of ordinary congestive failure. Pulsus paradoxus, a sign of secondary importance, is not infrequently observed in constrictive pericarditis, where its presence may be ascribed to adhesions or to kinking of the large mediastinal vessels during inspiration. Inspiratory filling of the cervical veins, frequently observed in this disease, is not specific for the condition, being a frequent finding in congestive failure where it also represents a "squeezing out" effect of the liver by the inspiratory descent of the diaphragm. Hypoproteinemia is a frequent end-result, due to the chronicity of the condition, loss of protein due to repeated paracenteses and congestive albuminuria. This enhances the anasarca, and eventually leads to marked general bodily emaciation in

curious contrast to the disproportionate size of the protuberant abdomens of these patients. The patients complain of weakness, and may even present symptoms of abdominal visceral disease, as was observed in several of our cases who were even subjected to laparotomies. The respiratory distress, so characteristically observed in congestive heart failure, is relatively slight as compared with the signs of systemic congestion. In Case 3, where dyspnea and orthopnea were prominent symptoms, co-existing cardiovalvular disease was present. The absence of severe respiratory symptoms is largely due to the fact that both ventricles are encased and that the congestion is predominantly retrograde from the right heart. It is conceivable, however, that pulmonary congestion will occur if the compression is predominantly over the left ventricle. It is our impression that in our series constriction of both ventricles played the dominant role in the genesis of symptoms and that constriction of the auricles and great veins if also present, did not materially affect the circulatory dynamics.

The electrocardiograms of these cases showed low voltage of the deflections, and not infrequently inversion of the T waves. In some cases there was evidence of right axis deviation, and a fixation of the electrical axis on change of posture. In general such electrocardiograms with low voltage in all the ventricular complexes indicate poor myocardial function and are seen in other circulatory conditions in which there is no suspicion of constrictive pericarditis. These electrocardiographic changes are a useful aid in the diagnosis, and in isolated cases there has been "electrocardiographic improvement" after the operative release of the heart, but on the whole these electrocardiographic signs do not compare in value with those of the "triad of Beck."

Ascites is one of the characteristic symptoms of chronic constrictive pericarditis. The clinical picture of this disease is not complete until the ascites appears. The fluid is usually a transudate. The ascites frequently elevates the venous hypertension and when the fluid is removed, there is a corresponding fall in venous pressure. The ascites frequently appears long before the peripheral edema. The reason for this is not certain, but it is our impression that in view of the perihepatitis and the resistance of the liver to back pressure from the heart, there is a disproportionate elevation of the hepatic and portal pressure as compared with the inferior venae cavae hypertension, which leads, therefore, to the earlier appearance of the ascites as compared with the peripheral edema, or anasarca.

Circulatory measurements, with the exception of those of the venous and the arterial pressure, have only a limited application in the diagnosis of chronic constrictive pericarditis. The ether and the saccharine time may indicate the presence of a circulatory disturbance and also the segment of the circulation in which the blood flow is delayed, but such observations may obtain in all cases of heart failure, whatever may be the cause. The cardiac output is diminished, as was proven in the single case of our series in which it was tested (by the Grollman method).

The initial venous pressure is usually elevated, at times reaching over 30 cm. in height. The venous hypertension may be regarded as the most significant finding in chronic constrictive pericarditis; it may persist even in the presence of clinical improvement. In several of our cases the increased venous pressure persisted even after operation in spite of symptomatic improvement, especially the disappearance of the ascites. The venous hypertension gradually returned to normal in two of the cases, but it persisted in three of the others. It should be remembered that the incarcerated myocardium atrophies and the myocardial efficiency does not return for weeks or months after the heart has been released.

One of us (W. M. H.) has observed the effect of right upper abdominal compression on the height of the initial venous pressure in six of the cases reported. In all of the cases there was a marked rise of from 10 to 20 cm. above the initial venous pressure level when the abdomen was compressed for one minute. This venous pressure curve is identical with that obtained in right heart failure from other causes. It is of great value in the diagnosis of chronic constrictive pericarditis because even when the initial venous pressure is lowered to within the normal range after removal of the ascites, the venous pressure curve characteristic of right heart failure (i.e. the marked rise of the venous pressure on right upper abdominal compression) persists. This was illustrated in Case 7. This observation was successfully applied to a case which presented the features of chronic constrictive pericarditis but which, on operation, proved to be a case of simple polyserositis. The case was intentionally not included in the series of cases of constrictive pericarditis. In this case the diagnosis of chronic constrictive pericarditis was not favored because the initial venous pressure, which was slightly above normal, became lower on right upper abdominal compression, a phenomenon which obtains in normal individuals and was never observed in our proven cases of constrictive pericarditis.

SURGICAL ASPECTS

The direct operative approach which has been advocated for constrictive pericarditis has consisted essentially in an extrapleural exposure of the heart, release of the right heart with special dissection at the venae cavae *after* release of the left heart, and completion of the removal of the constricting membranes in a one-stage operation. In our early experiences, an effort was made to follow closely the plan of operative treatment which had been laid down. Subsequently, divergence in three particulars appeared warranted. 1) Routine release of the right heart with special reference to the right auricle and the superior and inferior vena cava had been advocated for a specific and obvious reason. We found, however, that identification of the right heart as such was not easy and might even be impossible, that dissection over the right auricle and cavae was dangerous at times, and that as a matter of experience, definitive and lasting results could be achieved without release of the right auricle and adjacent

venous trunks. 2) Although painstaking efforts at extrapleural exposure of the thickened pericardium were made, inadvertent openings into the pleura usually occurred, in our experience, at some stage of the operation. This has also been reported by others. Not only were pleural openings difficult or impossible of closure but also the attempted extrapleural operation was found to offer too limited an exposure. As a result, a definitively transpleural operative exposure was favored. This approach has been employed in all cases (five in number) since 1936. 3) Classical cases of constrictive pericarditis unquestionably lend themselves to a single stage procedure. The heart truly escapes from its confining membrane, immediate improvement in heart action usually sets in, and there is therefore every incentive to proceed with completion of the release of the heart at a single operation. There are cases, however, in which doubt exists as to how far one may proceed safely at operation. In such instances possible additional decortication in a second stage appeared worthy of consideration. There are also cases in which typical constrictive pericarditis is not encountered at operation and in which therefore pericardiectomy may be of doubtful value. In such instances too extensive decortication seemed unwise; the results of a partial operation could be awaited and a second stage proceeded with, if indicated. Thus, we have favored and practised on occasion a two-stage operation and advocate it under the foregoing circumstances.

Despite considerable experience with the operative treatment of the disease, we remain in doubt as to how much of the diseased pericardium should be excised in some cases. We believe that excision should be generous over the right heart although there is usually no special reason for dissection over the right auricle and venae cavae. Excision over the left heart must be extended to the posterior surface of the organ. It is our practise to excise in this region as well as over the diaphragm until the heart, including the apex, is well released. However, the extent of excision on the posterior surface and to the extreme right has varied in different cases and, as we have said, we remain in doubt as to how nearly complete it should be. Reformation of a constricting membrane after excision need never be feared if enough has been removed to release the heart since the source of the fibrous tissue, the diseased pericardium, will have been removed.

SUMMARY

The histories of a series of eight cases of chronic constrictive pericarditis that came to operation have been epitomized in the foregoing paper. Two of the patients died and brief summaries of the necropsy findings are reported. From a medical standpoint, the diagnosis can usually be arrived at, sometimes readily, sometimes only with the aid of special studies of the dynamics of the circulation. As the medical treatment is admittedly

only palliative, we are convinced that all cases should be operated upon after careful preparation. In those cases in which the diagnosis after sufficient study is still somewhat doubtful, but in which the course is progressively downhill, we believe an exploratory thoracotomy with or without pericardiotomy, should be undertaken. The experience in the surgery of this condition has led to the view that the transpleural route is the best, as it affords an opportunity to decorticate the posterior cardiac surface partially, as well as to release the anterior surface of the heart. In several cases the decortication had to be divided into two stages, but the ideal has been to complete the release of the heart in a single operation. The final results of the operative treatment have been good in most cases, and in some instances have exceeded any pre-operative expectation. Chronic constrictive pericarditis is still the one chronic cardiac disease in which it has been established that practically every case should be operated upon, and that the condition can be cured by operation and only by operation.

THE PHYSIOLOGICAL BASIS OF THE EARLY TREATMENT OF INJURIES

HEINRICH F. WOLF, M.D.

If one studies the development of most forms of therapy, one must be impressed with the fact that definite cycles occur in the use of nearly all therapeutic methods. The question arises, "how is it possible that a method is hailed today as highly effective and is considered worthless tomorrow; that it will be taken up again with enthusiasm a few years later, only to be discarded again?"

The method is the same, the patients are not essentially different and still there are such striking changes in its application.

If we look closely at the main factors, we shall find that such changes in therapy are found only when it has been built on an empirical basis. If we do not know the pathological physiology underlying the disorder, nor the physiological action of our methods, we are bound to misjudge the causal connection between the treatment and the therapeutic success. Every therapeutic procedure if it is to be applied scientifically and to promise permanent progress in therapy must be based on sound physiological principles.

Statistics are not cited here. No two fractures are alike. Taking into consideration the infinite variety in the constitution of the individual one can readily understand that statistics are often misleading. For this reason unanimity or routine procedure cannot exist in injuries. Statistics lose much of their value because their authors give the good results but do not dwell enough on the failures. This failure to approach so many clinical problems from a basic physiological standpoint alone can explain the peculiar difference in the methods of treatment of injuries, particularly fractures, and especially as far as the use of physical therapy is concerned.

I do not intend to go back to the recommendations of Lucas Championnière and Mennell but shall restrict myself to the newest forms of treatment. While some authors maintain that physical therapy is effective only in the early stages, others recommend it only in the older forms and Boehler disregards physical therapy altogether. Admitted that Boehler's method of reduction under local anesthesia is a good one and gives excellent results, does his method also affect the injuries to the soft tissues which are always present? Do these need any attention?

It does not seem logical to disregard methods which aid the basic surgical treatment just to show that one can get along without them. Whether

to use physical therapy early or late can and should be decided on purely scientific grounds and not on empiricism. The engineer follows his blueprints in erecting a structure because he knows the mechanical facts upon which the safety of the structure depends. The modern physician should follow this principle as far as possible. Our blueprints are physiological and pathological facts.

This point of view does not only apply to fractures, but to all injuries. It would seem obvious that an injury to a healthy individual would offer more or less the same problem in nearly every case, depending only on the location and the type of tissue, and consequently therapy should follow the same physiological principles. Still, we find that the treatment of injuries varies with various physicians from complete omission (rest) to very active methods from the onset of the disease. To the impartial observer it appears that a way must exist by which the procedures are selected according to exact indications. Fortunately this is the case, as the physiological action of the modalities as well as the pathology of the injury are known.

Every injury is accompanied by a rupture of blood vessels, capillaries, arterioles, etc., and therefore, hemorrhages into the tissues occur, the amount depending on the severity of injury and the size of the ruptured vessels. The greater the hemorrhage, the greater, under otherwise equal conditions, the necessary repairs. It is surprising to find even in surgical text books the suggestion to use hot water applications immediately after an injury, a treatment which dilates the blood vessels and must naturally increase the hemorrhage. Only ice-cold compresses are indicated, though sometimes they may greatly increase muscle spasms. In that case they should be discarded (without using heat).

Not only the extent of a hemorrhage is of importance, but also its age. The longer we wait with the removal of the wreckage, the more it becomes organized, fibrosed and the longer it will take to remove it. Debridement is an accepted method of surgery in open wounds in which tissues have been crushed, partly or totally devitalized. However, in closed wounds tissue cells have also been destroyed and they must be absorbed. The necessity of this, a process which I call *internal debridement*, has never been properly envisaged, though Ashoff has clearly pointed out the reason and, therefore, the necessity of doing so. The sooner we try to remove the tissue debris, the more easily it can be done and the less we have to rely on the reparative processes of the body.

From this point of view it does not matter what kind of injury we are dealing with if the skin is unbroken, whether it is a contusion with a subcutaneous hemorrhage, a tear in the muscle, a dislocation or a fracture.

The method for removing the debris is massage. There is no reason whatsoever to wait with gentle massage in cases of contusions, but neither should it be delayed in cases of reduced dislocations. A joint once reduced

is often held tighter on account of the reflex spasm. No danger exists to dislocate it by gentle massage, no matter how long continued. It has always puzzled me why surgeons do wait. Why wait until adhesions form and the motions become mechanically restricted?

Dr. Howard Lilienthal has often referred such cases to me and they responded splendidly just because we started the massage immediately. Every case of dislocation treated by early massage will be completely restored within two weeks with the exception of dislocation of the knee joint complicated by complete tear of the lateral ligaments. For this, of course, complete immobilization is imperative.

In cases of fractures the time for starting the internal debridement is determined by the type of fracture. Here the indication set by the necessity of obtaining a good alignment and good union is paramount.

First of all the size of the fragment and its location is of importance. We are in the habit of speaking of a fracture whenever the continuity of a bone is disrupted. This is correct from an epistomological point of view but wrong from the clinical one. It makes a great difference whether the fracture is confined to a small part which does not interfere with the function or is in the shaft of the bone. On the other hand even a small fragment might cause severe disability if it is allowed to become attached to the bone in such a way as to obstruct motion mechanically.

In many cases, however, it does not matter at all if a fragment is disregarded completely and the injury treated as if only the soft tissue were involved. A few illustrations may suffice. I had occasion to treat two cases of fracture of a transverse process of the lumbar vertebrae from the day of the injury. Long, gentle massage was started immediately and both cases were entirely symptom-free and able to resume exercise, including horseback riding, ten days after the injury.

I have seen three cases of fracture of the greater tuberosity of the humerus, in one case complicated by a dislocation of the shoulder joint. In each case (after the reduction of the dislocation) massage was started immediately and in each case the function had been restored between ten and twenty-one days. It is not claimed that the small fragment had become attached to the bone again—what of it? Surgeons have been obliged to remove parts of a bone without disturbing the function. It is important only to carry off the wreckage by massage as quickly and as thoroughly as possible to reduce to a minimum the reparative inflammation.

Impacted fractures demand special consideration. I have seen many times that efforts were made first to mobilize and then reset such fractures. After strong efforts and increased traumatization, the radiographs failed to show the slightest change in position. In fact, we ought to consider impaction as an internal splinting and unless the displacement is severe and threatens to disturb the contour and the form of the limb (deviation),

impaction should be considered an advantage and not be disturbed. Our attention should be directed exclusively to the removal of the wreckage and the relief of pain.

But even if surgical interference, setting of the fracture, is imperative a delay of two or three days in the setting may be of advantage in most cases in which the hemorrhage inside of the fascia threatens to interfere with the venous outflow causing considerable edema, i.e., in the forearm or the leg.

Of the circulatory disturbances, Volkmann's ischemic contracture is one of the most dreaded. Even if it is not severe enough to cause a "*main en griffe*", the destruction of the nerves and muscles, the edema in the forearm and also in the leg causes a very protracted recovery, and at best necessitates a removal and reapplication of the cast. If, on the other hand, the extremity is immobilized on an open splint and immediate long, frequent, gentle massage is instituted, the hemorrhage can be removed from the tissues, the edema which is due to the pressure on the veins is quickly reduced and not only are the dangers of ischemia avoided, but the chance for a correct setting of the fracture is improved.

SUMMARY

1. We have spoken only of massage because massage is the sovereign method in the early cases of fracture, and in fact the only feasable modality.

2. The reason why massage is not sufficiently used is due to the lack of understanding by the technicians of the action of this treatment. Only very gentle effleurage is permissible. It must be painless, and given carefully. No other technique can be applied. Effleurage opens the capillaries, empties the veins and removes mechanically the wreckage consisting of blood and destroyed cells. It relieves the muscle spasms almost instantaneously, more quickly than heat applications and without increasing the active hyperemia by dilating the arteries.

3. We must learn to distinguish between massage and rubbing and we must realize the physiological action of the former.

4. Injuries cause hemorrhage and destroy tissue cells. The more quickly they are removed, the more rapidly will the injury heal and function be restored. To wait until nature does its job, and perhaps does it badly, indicates a disregard of physiological principles and means to delay recovery.

5. We have intentionally left out of discussion the use of various heat modalities, which are indicated only after a few days have passed and the torn blood vessels are safely closed. But even then, heat procedures only pave the way for massage which is the most efficient way to remove the wreckage. Heat just keeps the passages open.

RECOVERY FROM MENINGOCOCCEMIA AND MENINGOCOCCUS ENDOCARDITIS FOLLOWING ANAPHYLACTIC SHOCK

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The dramatic results achieved with the new chemotherapeutic drugs in the control of infections are apt to channel medical thought in one direction. We shall be inclined to forget that the immune reactions of the host still play the primary rôle in overcoming infection, even though the final result may often depend upon a chemical adjuvant.

The universal employment of sulfapyridine has served to obscure the equally dramatic crisis which signalizes spontaneous recovery in lobar pneumonia. Because of sulfanilamide, sulfathiazol, and other chemical agents, physicians in the future will rarely encounter an experience similar to the one reported. A prechemotherapeutic experience seems worth recording at this time because it illustrates that an insignificant physical or chemical agent is sometimes capable of setting off what might be called an immunological trigger mechanism and result in sudden control of a previously overwhelming infection.

CASE REPORT

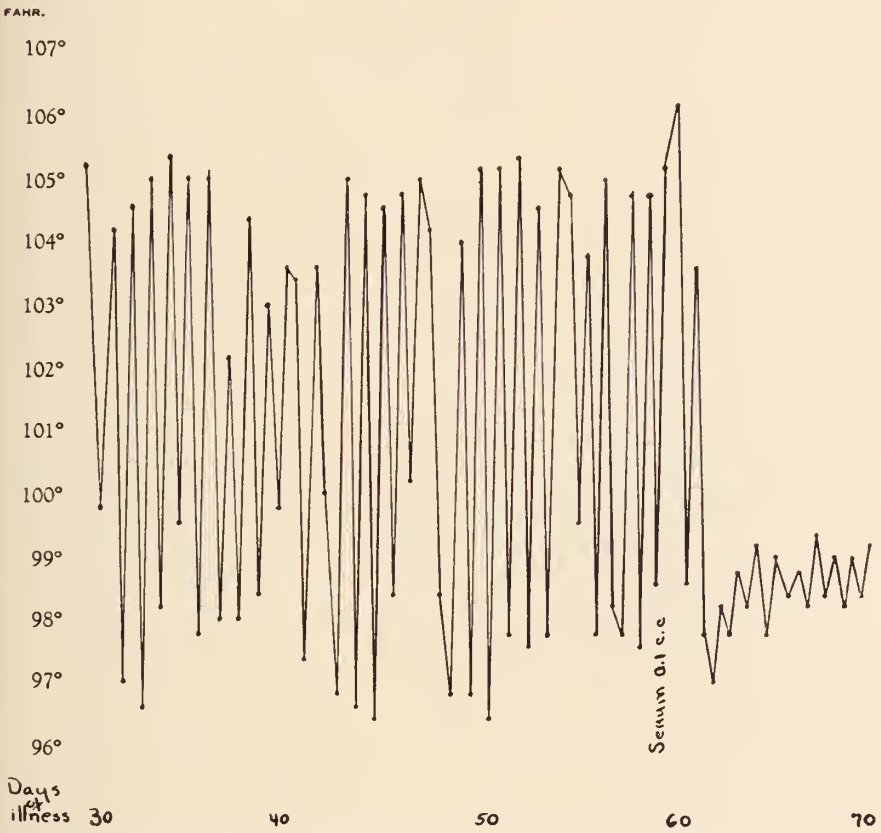
History. The patient was a girl of 13 years who had always been well except for childhood diseases, pertussis at 6 months of age, measles at 2 years and scarlet fever at 10 years. She was referred to me four weeks after the onset of the present illness, an obscure infection, the nature of which had not been determined. The illness had begun with fever, general malaise and headache. On the third day, a red macular eruption had appeared on the face and on the volar and dorsal surfaces of the extremities. The temperature swung daily between 101° or 102°F. in the morning and a peak of 104° to 105.6°F. each afternoon. New crops of small macules continued to appear every few days on the face and extremities and less commonly on the trunk. Some were raised and did not blanch completely upon pressure. At times some of the macules were distinctly hemorrhagic.

The patient had been under observation in a hospital in her community, where three blood cultures proved to be sterile and no clue to the nature of the infection was discovered. She was referred to me for investigation and transferred to The Mount Sinai Hospital after the illness had lasted four weeks.

Examination. At that time, examination revealed no abnormalities in the eyes, ears, nose or throat. There were no lesions on the mucous membranes. The regional lymph nodes were not enlarged. The heart was of normal size and configuration, the sounds were of good quality and there were no murmurs. The rate was rapid, 120 per minute and regular. The pulmonic second sound was slightly accentuated. No abnormalities could be detected in the lungs. The liver was not palpable and did not appear to be

enlarged. The spleen was enlarged so that its firm edge was palpable one centimeter below the costal margin. The blood pressure was 100 systolic and 68 diastolic.

On the flexor and extensor surfaces of both upper and lower extremities and on the buttocks, numerous erythematous macules were to be seen. Some of the most recent lesions were slightly, but definitely raised, as if infiltrated. The majority were flat and fading. On the face a few scattered fresh lesions were present.



Compressed temperature chart for a period of six weeks, illustrating the daily fluctuations in temperature due to meningococcus endocarditis.

Normal temperature and immediate disappearance of bacteremia of ten weeks duration followed intravenous injection of 0.1 cc. (1½ drops) of anti-meningococcus horse serum to which the patient was sensitive.

Laboratory Data. The blood count presented a moderate leucocytosis. The hemoglobin was 85 per cent, the red blood cells 4,600,000, white blood cells 18,750 (mature polynuclear neutrophiles 63 per cent, staff cells 2 per cent, mononuclear cells 3 per cent and lymphocytes 32 per cent). The urine contained a faint trace of albumin and microscopically an occasional leukocyte, hyaline cast and an uncommon red blood cell. X-ray examination of the chest was negative; the lung fields were clear and the heart presented a normal outline except for a slight prominence of the pulmonary conus.

Course. During the next five weeks, a septic type of fever continued, the temperature rising from normal or subnormal in the morning to 104° or even 105.8°F. in the

afternoon. Fresh crops of macules continued to reappear on various parts of the face and extremities and occasionally on the chest. Some were hemorrhagic. The child presented the picture of a severe bacteremia, but repeated blood cultures were negative.

On the seventh day after admission, five weeks after the onset, a cardiac murmur first became audible. A systolic murmur which increased steadily in intensity for several days could be heard over the second and third interspace to the left of the sternum. By the end of the sixth week of the illness, the murmur was loud. The heart rate was now 150 per minute. The lungs remained clear. The splenic enlargement was somewhat more pronounced. New skin lesions appeared on the wrists and forearms. Some of the new macules were distinctly purpuric. For a few days, the patient complained of vague pains in the wrists but no swelling was evident.

At this time, the hemoglobin was 88 per cent, the red cell count was 4,800,000; the leukocyte count 11,800, platelets 270,000, segmented polynuclear neutrophiles 68 per cent, staff cells 15 per cent, lymphocytes 12 per cent, monocytes 5 per cent. Agglutination tests for typhoid, paratyphoid and undulant fever were negative.

Five blood cultures had been reported as negative and yet it was clinically apparent that the patient must have an endocarditis with bacteremia. One possible explanation was that the endocarditis was located on the pulmonary valve and that the organisms were filtered out by the lungs. The absence of any abnormal signs in the lungs militated against this possibility. If the endocarditis were located on the mitral valve or the wall of the left auricle, the negative blood cultures could be due only to the fact that the organism was difficult to grow.

Because of the hemorrhagic character of the macular rash and the fact that the blood infection and endocarditis had now lasted nine weeks, it was felt that the organism was probably a gram-negative coccus, either a gonococcus or a meningococcus. The bacterial laboratory was, therefore, asked to use more blood as well as serum in the next blood culture. The sixth blood culture taken nine weeks after the onset of the illness was reported positive and meningococci were recovered from three flasks.

Up to this time, and in the absence of a positive culture, non-specific therapy had been employed. For three weeks, typhoid vaccine had been injected intravenously every three or four days beginning with five million bacteria and doubling the subsequent doses, but without any influence upon the clinical course. As had been anticipated, the finding of meningococci in the blood stream explained the petechial character of the rash.

As this illness occurred in 1934, before the days of sulfanilamide, the specific therapy consisted in the intravenous administration of adequate amounts of anti-meningococcus serum. Unfortunately, the patient proved on intradermal test to be extremely sensitive to horse serum. By the end of the tenth week of the illness, it appeared that the patient was doomed to die. The general condition was rapidly deteriorating, the pulse rate was more rapid and the temperature soared as high as 105.8°F. Because a fatal outcome seemed inevitable, it was determined to make an attempt to desensitize the patient in order that serum might be employed.

With this idea in mind, a minute dose of serum, 0.1 cubic centimeters (one and a half drops) diluted in 5 cubic centimeters of sterile saline solution was injected intravenously. Within a minute, the child became deathly pale and pulseless and looked as if she were about to die. It was apparent that she was in profound anaphylactic shock. Adrenalin was immediately administered both intramuscularly and intravenously, following which she revived. There then occurred a severe chill lasting almost an hour at the end of which the temperature was recorded as 106.4°F. However, it began to drop rapidly, with a drenching sweat, and within two hours reached 98.8°F. During the night, six hours after the injection a second chill occurred which was followed by a final rise in temperature to 103.8°F. The temperature again dropped steadily reaching 98.6°F. by noon and 98.0°F. by 4 p.m.

From that time, the temperature remained absolutely normal. Within twenty-four hours the child began to look and act well except for weakness. No further eruption appeared on the skin. However, a soft systolic murmur persisted over the pulmonic area. Ten days after the incident, the patient was able to walk out of the hospital.

DISCUSSION

A sudden and dramatic recovery had occurred from what appeared at the time to be a fatal infection with meningococci. After an illness of ten weeks and at a time when a fatal issue appeared imminent, anaphylactic shock followed by a chill and temperature of 106.4°F. resulted in immediate and complete sterilization of the infection. Although spontaneous recovery from meningococcemia and meningococcus endocarditis are not rare, no such outcome could have been expected in this instance.

Hyperpyrexia (106.4°F.) may have played a rôle for gram-negative cocci are unusually thermolabile. However, the temperature had repeatedly been as high as 105.8°F. without any influence whatever upon the clinical course. During the ten weeks of illness, the immunologic forces of the body had been unable to reach a concentration adequate to overcome the infection. The sudden and almost fatal anaphylactic shock, and perhaps the severe rigor and pyrexia which followed, had a rapid and profound influence upon the balance between the infection and the forces of recovery. The dramatic influence of a drop and a half of serum is regarded as due primarily to the anaphylactic phenomenon.

LIPOMA OF THE MESENTERY IN A CHILD AGED TWO YEARS

MURRAY H. BASS, M.D.

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The following case is being reported, first because of the curious clinical history, secondly because of the difficulty in diagnosis, and thirdly because of the extreme rarity of the condition found at operation.

CASE REPORT

History. James R. was born in May, 1938. He was the second child of healthy parents. There is no family history of allergy or of tuberculosis. Birth was normal. The only abnormality noted soon after birth was a definite systolic cardiac murmur heard best over the mid-sternal area.

I saw the infant first on March 22, 1940. He was twenty-two months old and was brought for a general examination because of an upper respiratory infection. At that time he weighed $26\frac{3}{4}$ pounds, stood and walked, and appeared well developed. He said one or two words. There was no evidence of rickets or anemia. The cardiac murmur was present; there was no clubbing or cyanosis.

Examination. I was again asked to examine the baby on May 13, 1940 and was given the following history: On and off, during the previous year the child had been seen to get on his hands and knees and rock back and forth. During such periods he would knock his head rhythmically against the side of the bed each time he rocked forward. On the day I saw him, he had vomited several times, and had started such a rocking attack at about 6 P.M.; still continuing at 8 P.M. The child appeared distressed. His face was pale and his hands clammy. If one took him out of bed and put him on the floor he crept over to the wall and immediately started to rock, hitting his head against the wall with every forward movement. He moved back and forth so fast that he was almost a blur. When we stopped him and sat him up, he would grab at his abdomen and rub his fingers up and down over its surface from the costal margins to the pelvis. He did this so hard that the abdominal skin was covered with deep parallel vertical scratch marks.

The remainder of the physical examination was entirely negative. The pulse was very rapid but quite regular. The temperature was normal. Palpation of the abdomen was difficult, but it was soft and no mass could be felt. Rectal examination was negative.

It appeared that the child was experiencing severe abdominal discomfort. During the rocking episodes he emitted a short grunt, synchronous with the forward motion, which resembled the sound one hears emitted by patients with abdominal cramps. The mother stated that for the past fortnight the child had not eaten as well as usual and had occasionally vomited. His bowel movements were regular and normal.

A sedative was given and the rocking subsided. The following day a blood count was done and found perfectly normal. A patch test for tuberculosis was negative. Urine and stool examinations were normal. The abdomen was again carefully palpated this time while the child was quiet and cooperative. It was soft, not distended, there was no evidence of visible peristalsis, and no masses could be palpated.

A few days later the child had another attack of vomiting, pallor, rocking and

grunting. On account of the rubbing and scratching of the abdominal wall, we were led to believe that the baby must be suffering from some form of abdominal pain and for this reason a barium meal was given and radiograms taken. The report of the roentgenologist, Dr. William Snow, follows:

"Barium meal showed the following: Oesophagus, no abnormality noted. Stomach, normal. Duodenum, normal. Small intestines, proximal loops of jejunum are displaced from the left to the right outlining a very large rounded zone which could be produced by a mass, possibly retroperitoneal. The lower loops of ileum are displaced high into the abdomen by distended bladder. These observations were noted

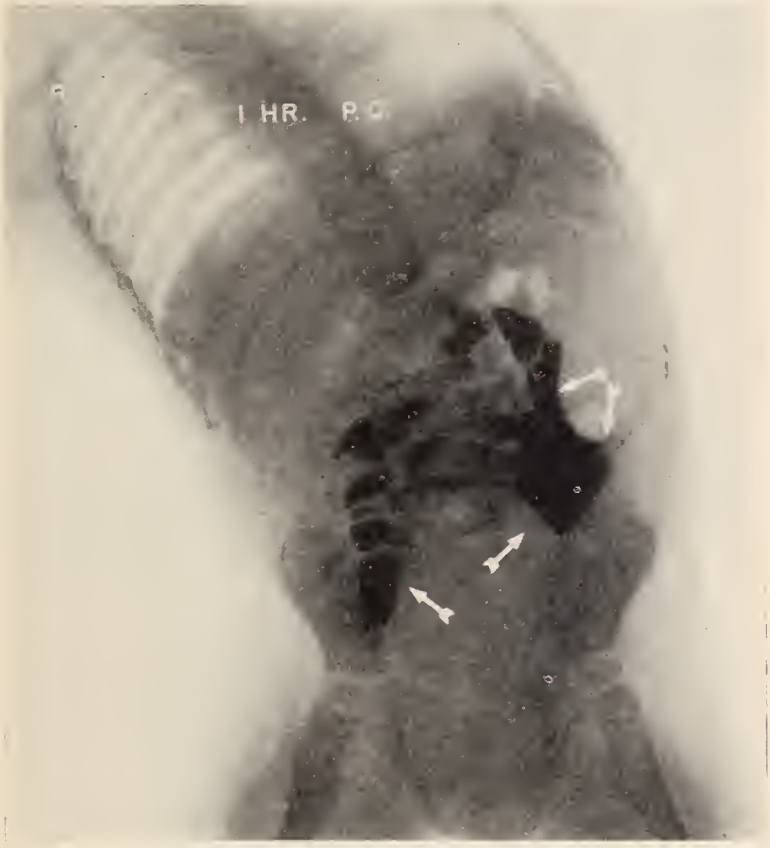

FIG. 1. Radiograph of abdomen taken one hour after barium meal. Arrows point to displacement of gut.

at varying intervals during the morning of the examination. Large intestines, at six hours none of the barium had reached the colon. At twenty-four hours the colon was irregularly filled from cecum to rectum. No abnormality was noted. There had been two bowel movements.

The above findings may be indirect evidence of the presence of congenital malformation in the urinary tract indicated by a large bladder and large left kidney. If an obstructive lesion is present it should be at the neck of the bladder or in the urethra. I cannot fit this in with a small kidney on the right. It is also possible that the bladder is accidentally filled and that the mass on the left is of other origin.

Examination of the ehest shows no abnormality of the heart or lungs" (Figs. 1 & 2).

After reeeiving this report the abdomen was again palpated but we were unable to feel any mass.

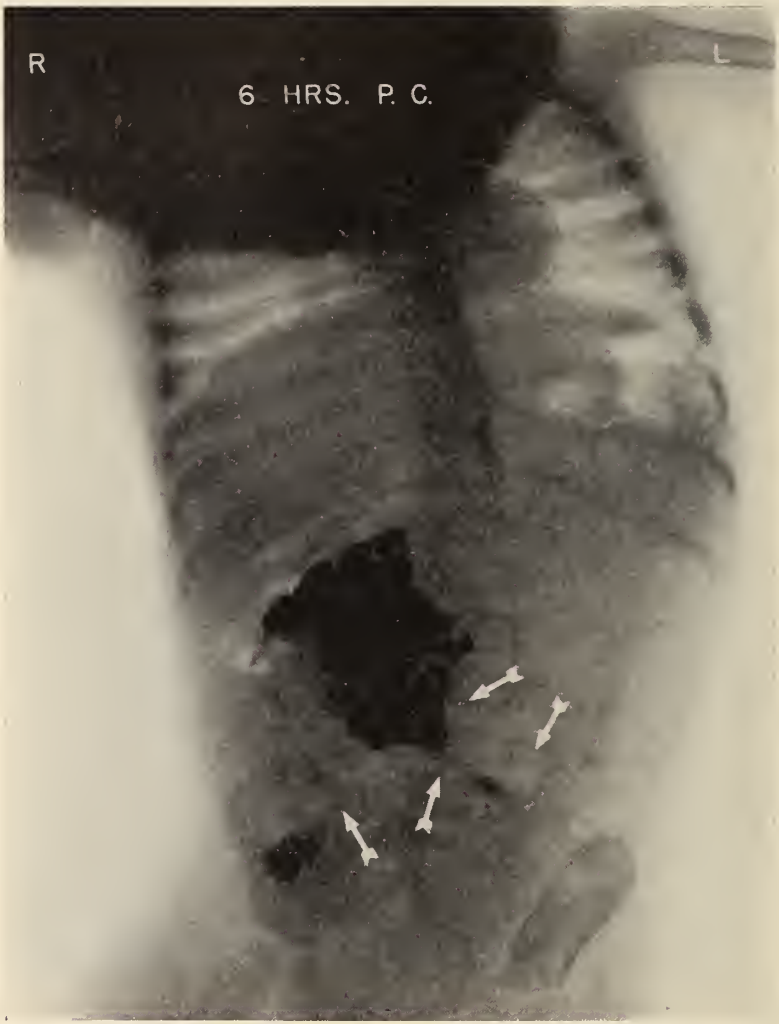

Fig. 2. Radiograph of abdomen taken six hours after barium meal. Note that the gut is still displaeed and that there is no filling of the large gut.

On aceount of the presenee of a eongenital eardiae lesion, we thought there might be another anomaly in the abdomen, possibly a ptosed eongenitally hydronephrotic kidney. The patient was therefore referred to Dr. A. Hyman for study. Before injecting Diodrast he examined the abdomen and felt a large rounded freely movable mass, the size of a large peaeh, in the left upper quadrant. The mass was not tender. Pyelography revealed perfeetly normal kidneys and ureters.

On being informed of the discovery of an abdominal tumor, I reexamined the

child that same evening. It was quiet and very cooperative and allowed thorough palpation without resistance. No mass could be felt. The same was the case on the following day. I then decided to examine the child under anesthesia. He was again examined by Dr. Hyman, who, at this time, could feel no mass. Under ethyl chloride anesthesia, however, a large, somewhat cystic, very movable tumor was felt in the left side of the abdomen.

With this definite finding, exploratory operation was decided upon and the child was referred to Dr. Louis Friedman. He also was unable to feel any abdominal condition until he had given an anesthetic, after which the tumor again became evident.

Our pre-operative diagnosis was mesenteric cyst. We reasoned that since several urine examinations showed normal findings and since pyelography was negative, we could rule out the urinary tract. Several examinations of the stool showed absence of blood and normal microscopic findings. This pointed against a growth in the gut itself. The extreme ease with which the tumor could be moved about in the abdomen and the fact that it slipped up under the liver or under the diaphragm so as not to be felt at all made the mesentery a likely site for the growth. All those who felt the mass agreed that it felt soft and elastic. Mesenteric cyst, then, seemed the most likely diagnosis.

Operation. The child was operated upon on June 6, 1940 by Dr. Friedman. Under ether anesthesia the tumor was, this time, felt in the right lower quadrant where the operative incision was made. The following is the surgeon's description: "Right rectus incision. Upon opening the peritoneum no fluid was encountered. A large grape-fruit-sized mass was found and proved to be a multilocular lipoma of the mesentery of the small intestine situated about ten to twelve inches from the ileocecal junction. This lipoma was carefully dissected out after incising the very thin peritoneal leaf of the mesentery. This left about five inches of small bowel not covered by peritoneum at its mesenteric border. Because two or three spots in this piece of ileum seemed to be bluish and devoid of blood supply, it was deemed advisable to resect this portion of the bowel. This was done by closing the anal end of the loop using linen and then performing a lateral anastomosis, also using linen. The abdomen was closed without drainage.

Upon exploring the rest of the abdomen, no other masses of this kind were encountered. The small bowel was thinned out and spread over the tumor mass in a ribbon-like fashion. Because of this condition, the child's symptoms were evidently due to torsion of this freely movable tumor."

Postoperative Course. The patient stood the operative procedure very well; his pulse remained of good quality and his color was excellent. However the postoperative reaction was very violent. The temperature rose to 104°F. In spite of a continuous saline and glucose intravenous drip and a blood transfusion, the child's condition remained very poor. Restlessness was extreme and was not alleviated by codeine or large doses of barbiturates. About twenty-four hours after the operation he became deeply cyanosed and stuporous, with almost imperceptible pulse. Pulmonary edema set in and he was put in an oxygen tent. In spite of heroic stimulation with coramin, atropine, etc., the condition failed to improve though the coarse, bubbling râles in the chest had disappeared. The temperature remained high, the pulse 160 per minute, the respirations 52 per minute. Blood count at this time showed a white cell count of 8,050 with 65 per cent polynuclear leukocytes. The abdomen was soft and showed no evidence of peritonitis. The possibility of pneumonia was entertained and an X-ray examination of the chest was done. This revealed definite increase of the right hilus shadows with haziness over the entire right lower lobe, and was reported as an early pneumonia.

Since all fluid by mouth was vomited, we gave 1.0 Gm. of sulfapyridine by rectum,

repeating this so as to give about 2 gr. per lb. per day. To this drug the child reacted very favorably and by the end of the second day the temperature had dropped to 100°F. and his general condition had definitely improved. On the second and third postoperative days the upper abdomen became much distended and there was considerable emesis. This was relieved by gastric lavage which produced large amounts of bloody gastric fluid.

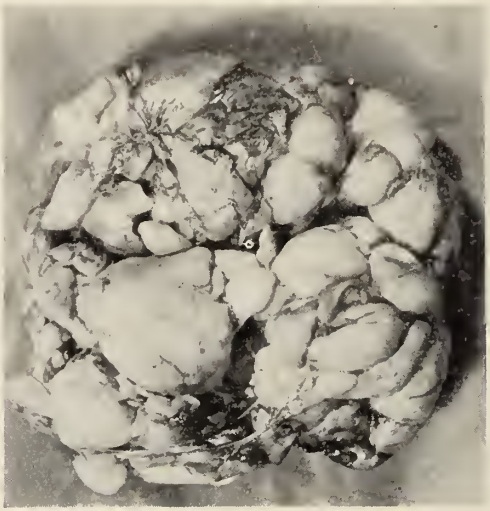

FIG. 3. Photograph of mesenteric lipoma after removal. Size 12 x 10 x 5 cms.

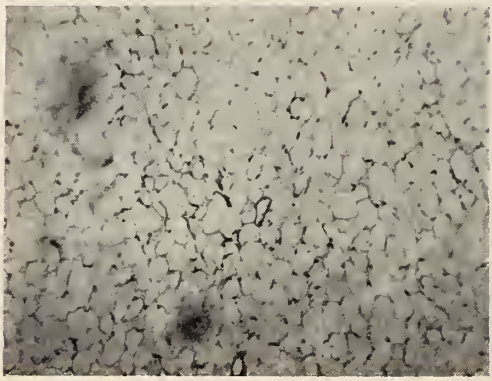

FIG. 4. Microscopic appearance of tumor

On the third postoperative day, the boy received a second blood transfusion of 200 cc. His condition gradually improved; he became quieter and his pulse became slower. On the fourth postoperative day the intravenous drip was stopped and he went on to a normal convalescence.

At the present date, two months after his operation, the child is in excellent condition. The rocking habit still persists, but he has no evidence of pain. Bowel movements are regular and the vomiting has ceased.

The pathologist's report of the tumor read as follows: The specimen is an irregu-

lar, fatty, tumor mass measuring in all approximately, 12 x 10 x 5 cm. It is irregularly lobulated with some of the lobules almost independent of the main mass (Fig. 3). On section, the specimen consists of adipose tissue throughout, subdivided by fine fibrous trabeculae.

Also received, is a resected segment of small intestine about 5.5 cm. in length. The mesenteric attachment has been ligated and separated, leaving the segment devoid of mesentery. The serosa is smooth but dark red in color, and in the center, somewhat bluish. The mucosa is markedly congested.

Numerous sections of the tumor mass show it to consist of essentially normal appearing fat tissue, subdivided by fine fibrous trabeculae (Fig. 4). The capsule is slightly thickened and mildly inflamed in a few places. Sections of the resected bowel show vascular engorgement, focal hemorrhagic extravasations, and edema, and mild degenerative changes of the muscularis.

Pathological Diagnosis: *Lipoma of mesentery.*

DISCUSSION

Tumors of the mesentery are of rare occurrence, particularly in children. They may be divided into the cystic and solid tumors, of which the former are more commonly encountered. The solid tumors arise from the connective tissue between the mesenteric leaves and may therefore appear as fibromata, lipomata, fibromyomata and sarcomata. The solid tumors are often the seat of inflammatory and degenerative processes, sometimes giving rise to pseudo-cysts, thus leading to confusion in diagnosis. Solid tumors of the mesentery are rarely encountered among children. Writing in 1932, J. E. Summers (1) was able to collect 128 cases reported up to that time, of which only 16 occurred in children. These were distributed as follows: fibroma, 2; lymphosarcoma, 3; round-celled sarcoma, 2; teratoma, 1; fibrous tissue, fat, cartilage, calcareous material, 1; malignant lymphoma, 1; lipoma, 1; fibromyxoma, 1; multiple fibromata, 1; angiosarcoma, 1; no data given, 2.

In a survey of the literature since 1932, I have been able to find but six cases of solid mesenteric tumors in children (2, 3, 4, 5, 6). Of these, two were fibroid tumors, one in an infant aged 6 days, and one in a girl aged 5 years; one, a fibrolipoma in a 10 year old girl; one, a lipoma in a boy aged 11 years; two, sarcomata in children aged respectively 4 and 5 years.

Among adults the most common type of solid mesenteric new growth appears to be the lipoma (7, 8, 9, 10). Such fatty tumors may arise in the mesentery itself or they may be the result of a "spreading out" of fatty tissue from the retroperitoneum, especially from the peri-renal fat. This gives rise to considerable confusion in the literature, such tumors being reported by some under the title "retroperitoneal lipoma", by others as "mesenteric lipoma." Certain authors (Jaki) attempt to classify lipomata on this basis. In my case, the tumor seems to have arisen in the mesentery itself and not to have grown forward from the retroperitoneal region. In childhood, this retroperitoneal type has also been described. Chown (11) has recently reported the case of a girl aged $3\frac{1}{2}$

years in whom an extraperitoneal lipoma weighing 4½ pounds was successfully removed. It was the surgeon's opinion that it arose in the pelvis.

How rarely this type of lipoma occurs in childhood may be gleaned from the following quotation from Sir L. Barrington Ward's "The Abdominal Surgery of Children" (p. 297) "Retroperitoneal Lipoma is a rare tumor. Eden and Lockyer say that they have found only one case (Lauwers') recorded in a child."

Lipomata may reach enormous dimensions, one of over 8 kilograms having been reported (5). The symptomatology of solid mesenteric tumors varies with their size and their position. Small tumors may cause no symptoms, one case being reported where the tumor was encountered in an operation for another condition. General discomfort, nausea, abdominal distress and constipation are commonly complained of. When the position of the tumor is close to the gut, symptoms of intestinal obstruction may make their appearance as in the case of d'Abrey (7) and my own case. Sometimes the only symptom is progressive enlargement of the abdomen. In this connection the case of Bergouignan (5) is of interest. An eleven and a half year old boy gave a history that in infancy he had had abdominal discomfort and vomiting. At three years of age an abdominal mass was discovered. Between the fourth and eighth year the boy's abdomen became enormously distended and the disease was considered to be tuberculous peritonitis or megacolon. Three years later the case was properly studied (X-ray, tuberculin and Wassermann tests) and operation was performed. A mesenteric lipoma with inflammatory changes was found occupying the entire abdomen, weighing over 8 kilos. The child made an excellent recovery.

In some of the adult cases the patient had known of the condition for as long as eighteen years before coming to operation. Other cases progress much more rapidly; thus in Summers' case of fibroma, rapid growth in the size of the tumor was noted by the mother during the month that elapsed between its first detection and the operation.

The diagnosis of mesenteric new growth is usually difficult. In my own case the extreme mobility of the tumor made us suspect it: for once the mass was felt, it could be easily moved about in the abdomen. Its mobility was emphasized by the fact that on each occasion when it was palpable, it was felt high up on the left side of the abdomen; when, however, the child came to operation, the mass was felt in the right lower quadrant. In spite of the fact that we were palpating through the thin abdominal wall of a two year old child, we were misled as to the character of the tumor, for, though it felt quite cystic, it turned out to be a lobulated, solid mass of fat.

In adults especially, mesenteric tumors may be confused with ovarian cysts, pancreatic cysts, abnormally situated kidneys, hydrops of the gall bladder and growths of the bowel. Many of the reported cases were

operated upon for various inflammatory conditions and various type of colic, such as renal, biliary or appendiceal.

The most characteristic quality of the mesenteric tumor, especially if seen before it reaches a great size, is its mobility.

The prognosis of these tumors depends on their type and whether they can be easily removed at operation. The benign types have, of course, a better outlook than the malignant. However, even the benign varieties have a tendency to local recurrence. In the sixteen cases of fibroma of the mesentery collected by Summers, twelve were operated on, eight recovered, and in four cases no data was given. Of the sixteen cases of all types of mesenteric tumors found in children, collected by the same author six died, five recovered and in five, no data were given. To these sixteen cases in children, I can now add six more from the literature and my own case. Of these, five recovered and two died.

There are thus, to date, twenty-three reported cases of solid mesenteric tumors in children with ten recoveries, eight deaths, and five with no data as to outcome.

The treatment is surgical and operation should be undertaken as soon as the diagnosis is made, first because the growth may be malignant or may become so, and secondly because intestinal obstruction may complicate the condition at any time. If at operation the tumor is found so close to the gut that its removal jeopardizes the gut's blood supply, as in our case, no chances should be taken and resection of the involved intestine should be done.

In conclusion, I want to emphasize the extreme rarity of mesenteric tumors in childhood and particularly of lipomata, my case being, I believe, the third one to be reported.

SUMMARY

A case of lipoma of the mesentery, successfully operated on, in a child, aged two years, is reported. From a survey of the literature it is found that this is an extremely rare condition in childhood. The pathology, symptomatology and treatment of mesenteric solid tumors is discussed.

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CARDIAC INFARCTION INDUCED BY UNUSUAL EFFORT

ERNST P. BOAS, M.D.

Last year I reported a series of cases of cardiac infarction accompanying unusual effort (1). The significance of this association in certain Workmen's Compensation cases was pointed out. In the states of New York and New Jersey, the workmen's compensation boards have allowed compensation to persons who experienced a cardiac infarction while engaged in some unusual strain while at work.

There has been some criticism of my conclusions, and in particular, it has been suggested that persons seeking compensation for injury are apt to tell untruthful stories, or at least to stretch the truth. It is for this reason that I am presenting three additional cases in which there appears to be an unequivocal relationship between the effort and the cardiac ininfarction, and in which compensation and litigation played no rôle.

CASE REPORTS

Case 1. History. R. G., a hotel manager aged 45 had been under my care since 1932. He had never had any serious illness, nor any symptoms or signs referable to any abnormality of the heart. While on his vacation in the fall of 1939 he played baseball. While batting at a ball he missed the ball and stumbled and fell on his buttocks. At first he thought he was unhurt, but a few minutes later, he began to experience substernal oppression and difficulty in breathing, and soon broke out in a cold sweat. The pain persisted for several hours until he received an injection of morphine. Precordial oppression lasted all night. I saw him two days later. The heart was somewhat enlarged, the heart sounds were very faint, the rate was rapid. The blood pressure was 84 systolic. The following day a pericardial friction rub was heard. Fever persisted for a week. The electrocardiogram revealed the classical picture of an infarction of the posterior aspect of the left ventricle. Two weeks after the onset of symptoms, right hemiplegia and aphasia occurred suddenly. The patient has remained with a very poor cardiac reserve, and a persistent hemiplegia and aphasia.

Case 2. History. J. B., a salesman aged 43, had always been well, strong and active. In 1937, he had obtained life insurance without difficulty. In 1939, while pitching a baseball he slipped and as he attempted forcibly to right himself, he experienced sudden sharp pain to the left of the sternum. He pitched one more ball, but by this time the pain had become severe, and radiated to the entire lower anterior chest and to the left arm. The pain persisted and after one and a half hours a hypodermic injection of morphine was given. There was fever on the second day. An electrocardiogram taken five days after the accident showed an acute infarction of the anterior aspect of the left ventricle. He was compelled to remain in bed for three months, and during this period, he had several additional attacks. I examined him six months after the original attack. The heart was much enlarged, the apex beat was forceful and diffuse, and the heart sounds were faint. Fluoroscopic examination confirmed the diagnosis of

aneurysm of the left ventricle, with paradoxical pulsation of the left border of the heart above the apex. The electrocardiogram gave evidence of old anterior and posterior infarctions.

Case 3. History. A. H., a 71 year old scientist, had always led an active life. He had had no symptoms referable to his heart, and in the year before his accident, he had been on a strenuous field trip. While travelling to Europe, he was promenading on the top deck. The steamer lurched, the deck became sharply inclined and he lost his balance. To steady himself, he caught a rope that was behind him, and as he continued to slide his body became twisted. With this jerky arrest of his fall he experienced for the first time a raw pain under the lower sternum. This lasted only a short time. The following morning he started to play shuffle board. The deck was wet, so it required unusual force to push the discs. At the first shove he experienced the same substernal pain, but it was more intense. He had to stop playing; the pain diminished, but persisted to some degree and was aggravated by walking. The following day after his arrival in London, substernal pain on effort persisted. The next day substernal pain increased and radiated down both forearms and he was compelled to enter a hospital where the diagnosis of coronary thrombosis was made and confirmed by Sir Thomas Lewis.

DISCUSSION

Cardiac infarction following a fall, as in Case 1, has been reported previously. A man while skiing fell on his back and immediately experienced substernal distress and infarction of the posterior aspect of the left ventricle (2). I have seen a number of other patients in whom a sudden forcible attempt at righting the body during a fall, as in Cases 2 and 3, has been immediately followed by a cardiac infarction.

There are a number of ways in which an unusual strain may alter cardiovascular dynamics to induce a cardiac infarction. The pathologic study of Horn and Finkelstein is illuminating (3). They found, in a study of one hundred hearts which at necropsy showed evidence of recent coronary occlusion, that the closure was produced by intramural hemorrhage in 62.5 per cent. The frequency of intramural hemorrhage as a cause of coronary occlusion has been pointed out before. Such hemorrhage occurs in a vascularized section of an atherosclerotic area in the arterial wall. It is easily comprehensible how a severe blow on the chest, a severe jar of the heart by contre-coup, or a sudden rise in blood pressure may induce a rupture of a coronary intramural capillary with subsequent intramural hemorrhage. Depending on the size of the hemorrhage and the speed with which the extravasated blood collects and occludes the arterial lumen, the full clinical picture of cardiac infarction may be immediate or delayed. Horn and Finkelstein found anatomic evidence that coronary artery occlusion may be a slow progressive process.

In Cases 1 and 2, the coronary closure was rapid, almost immediate. In Case 3, although injury to the coronary arterial wall was immediate, the total closure of the vessel was not completed until three days had elapsed. It is important to recognize the occurrence of such delayed closure.

In cases in which symptoms of coronary insufficiency appear for the the first time during physical effort or accompanying trauma, and in which the disabling cardiac infarction occurs some days after the accident, the infarction may be attributed to the trauma or effort.

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A CASE OF GENITAL APLASIA: ARTIFICIAL VAGINA SUCCESSFULLY CONSTRUCTED BY THE BALDWIN OPERATION

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AND

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A case of congenital absence of the vagina and uterus successfully treated by the Baldwin operation (for formation of an artificial vagina) is described for several reasons: It represents the only case of a Baldwin operation performed at The Mount Sinai Hospital; it gave an excellent result in spite of numerous, grave, postoperative complications; it draws attention to the presence of other congenital anomalies, serving to re-emphasize this frequently observed association; and finally it adds to the literature, another case of vaginal aplasia successfully treated by the Baldwin operation.

CASE REPORT

History. Miss H. J., aged 18, presented herself with the complaint that she had never menstruated. The family and past history were non-contributory except that the patient's mother had died during an epileptic seizure.

Examination: The patient displayed normal, well developed, female, secondary sex characteristics. Examination of the external genitalia revealed the presence of a normal clitoris and labia and the absence of a vagina. No uterus was palpable on bimanual rectal examination. A cervical rib was felt in the right cervical region, above the clavicle. A right upper dorsal scoliosis was also noted. Subsequent X-ray examinations revealed multiple congenital anomalies of ribs and dorsal spine (Fig. 1). These conditions apparently caused the patient no discomfort, no pressure symptoms being elicited.

A well healed appendectomy scar was present in the right lower quadrant of the abdomen, but neither the patient nor the family had ever been informed of any existing congenital abnormalities.

The dangers of the operative procedure were explained to the patient and her family but she was insistent on submitting to any ordeal in order to correct the existing defect.

She was admitted to the Semi-private Pavilion of The Mount Sinai Hospital on August 4, 1936, where, in addition to the above described positive findings, the urine analysis report revealed the following: Specific gravity, 1020; a trace of albumin; microscopic examination revealed many white and red blood cells. In view of the fact that the urine examined was a non-catheterized specimen, the report of a trace of albumin and many white blood cells was disregarded, and even though the presence of a moderate number of red blood cells could not be accounted for, these findings were not investigated pre-operatively, an oversight which should be emphasized. The explanation was found when an ectopic pyonephrotic kidney was discovered in the right side of the pelvis during operation.

The patient was of poor economic status and could not afford to submit to the long period of hospitalization usually required for the skin flap type of procedure. After considering the various methods hitherto employed for the construction of an artificial vagina, Dr. Bodenheimer felt that the Baldwin operation was the method of choice.

Operation. The operation was performed on August 5, 1936, under avertin anesthesia, in the following manner:

1. By sharp and blunt dissection a cavity was made between the urethra and bladder anteriorly and the rectum posteriorly. The dissection was carried up to the peritoneum and an Ochsner clamp placed in the cavity.

2. The peritoneal cavity was entered through a 6 inch left paramedian muscle splitting incision. An ectopic right kidney was present on the brim of the pelvis at the level of the upper sacral segment. The left kidney was normally situated. No uterus was found, but in its place was present a thin rudimentary cord-like structure. The ovaries

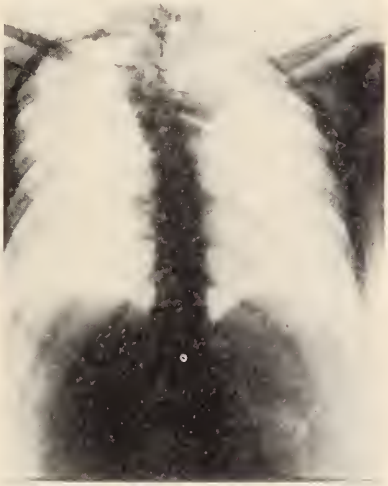

FIG. 1. Showing right cervical rib; synostosis of 2nd and 3rd ribs on the right side and 1st, 2nd, 3rd, 4th, and 5th ribs on the left side; multiple congenital anomalies of 2nd, 3rd, 4th, and 5th dorsal vertebrae with wedged bodies, partial fusion and angular scoliosis.

and tubes were normal in appearance but they were located as follows: The left adnexae were situated in the abdomen caudad to the left kidney. The right were located cephalad and to the right of the ectopic kidney above described. The peritoneal fold dorsal to the bladder was incised transversely and dissected so as to visualize the point of the Ochsner clamp previously inserted into the newly formed space. A 14 inch loop of terminal ileum was mobilized and isolated, preserving its mesenteric attachment intact. Each end of this loop was doubly clamped, divided, and all four cut ends were closed by two inverting layers of sutures. The continuity of the ileum was re-established by side to side ileo-ileostomy. The mid portion of the isolated ileal loop was then grasped by the Ochsner clamp and drawn down into the excavation between the bladder and rectum, care being taken to avoid undue tension on the mesentery. The loop was then peritonealized as well as possible with the previously dissected reflection of vesical peritoneum. The abdominal cavity was closed in layers reinforced with tension sutures.

3. The apex of the loop of bowel in the perineal wound was incised and opened, and then sutured to the skin of the vulva in the region corresponding to the normal location of the vaginal orifice, between the labia minora.

Postoperative Course. The postoperative course was stormy and eventful. In the first three postoperative days there was moderate abdominal distention and the temperature ranged from 101 to 104°F. On August 8, bilateral parotitis developed. From August 8, to August 10, the fever rose from 103.6 to 105.6°F. and the patient had a chill. The condition became progressively worse and the patient appeared critically ill. On August 10, treatment of the parotitis with a Radon pack was begun. A total dosage of 680 milligram hours was applied successively to the left and right parotid regions with remarkable improvement in the condition. On the ninth postoperative day (August 14, 1936), the patient complained of abdominal pain. Physical examination revealed the separation of the skin, fascia and peritoneum of the central portion of the wound through which a distended loop of small intestine was visible.

The patient was taken to the operating room immediately and under general anesthesia the protruding bowel was replaced in the peritoneal cavity and the entire abdominal wound resutured with thru-and-thru braided silk sutures. The patient was

FIG. 2. Retrograde pyelogram revealing right ectopic kidney

then put in the lithotomy position and the newly constructed vagina was examined. It was irrigated with sterile saline solution, yielding considerable yellow, loose fecal material. Two vaseline gauze drains were placed in the artificial vagina. The patient ran a stormy course for the three days following the above procedure. The temperature receded by lysis from 105 to 102°F. From August 18, to September 11, the patient's convalescence was found to be progressively uphill. The abdominal wound gradually healed by secondary union and the foul discharge gradually cleared up under the following treatment:

On August 20, sixteen days postoperatively the newly constructed vagina was gently irrigated with saline solution. On August 24, a sodium bicarbonate douche yielded a foul discharge. From August 26 to September 12, the patient had daily "vaginal" irrigations with potassium permanganate 1 to 10,000, hydrogen peroxide, and sodium bicarbonate solutions, the washings yielding slightly cloudy mucus secretions. The patient was discharged thirty-eight days after the original operation. The abdominal wound had healed by secondary union with the new "vagina" well formed, its introitus admitting two fingers. No spur crushing procedure between the folded intestinal loops was necessary.

Follow-Up. For the maintenance of dilatation, Tampax plugs were employed because they were easy to insert and, as they swelled, they acted as dilators.

Hormone assay of the patient's urine revealed the following:

	Prolan	Estrin
9/1/37	75 m.u.	3 r.u.
9/4/37	50 m.u.	6 r.u.
9/8/37	Neg.	Neg.

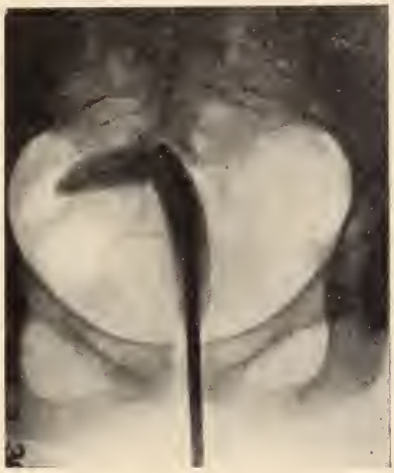

FIG. 3. Vaginogram using radio-opaque oil as the contrast medium

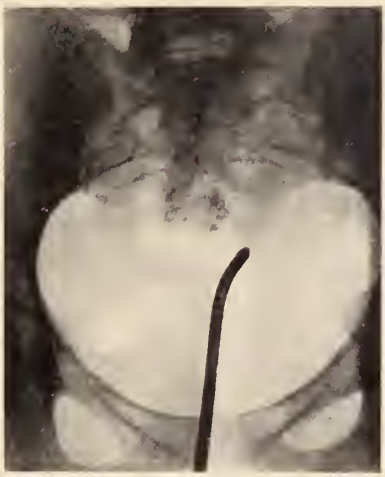

FIG. 4. Vaginogram using air as the contrast medium

On March 3, 1938, cystoscopy by Dr. Joseph Tenenbaum revealed the presence of a huge right ectopic pyonephrotic kidney with no indigo-carmine return in fifteen minutes (Fig. 2). The right kidney was situated on the right side of the pelvis. At subsequent examination the urine obtained from the right kidney by Dr. R. L. Dour-

mashkin was loaded with pus cells and culture revealed the presence of B. coli. The left kidney was normal. Both of the above-mentioned urologists advised right nephrectomy but the patient refused to submit to this operation. It may be pointed out that the pyonephrotic kidney was responsible for recurrent attacks of pyelitis as well as the severity of the postoperative reaction.

DISCUSSION

It will be recalled that this patient contemplated suicide prior to operation. The successful creation of a vagina made possible her marriage which took place on June 30, 1938. She reported satisfactory intercourse and orgasm. The satisfaction both mental and physical, which she enjoyed was reflected in her changed personality. The former melancholia, irritability and sense of inferiority no longer troubled her. The procedure of creating an artificial vagina is indicated in women who are about to be married, and in those single girls who have strong sexual desires. This particular patient is now pursuing a normal life which otherwise would have been denied to her. When last examined, her vagina was found to be four and a half inches deep. The introitus admitted one finger easily and two fingers with slight pressure. The vagina was large and roomy. Its fundus deviated to the right. This was ascribed to the upper curve of the intestinal loop. (See X-ray Vaginograms, Figures 3 and 4.)

SUMMARY

1. A case of congenital absence of the vagina treated by the Baldwin procedure with excellent plastic and functional result, is here described.

2. The necessity for pre-operative urologic investigation to discover possible associated renal lesions is suggested.

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THE NECESSITY FOR "TYPING" PNEUMONIAS[1]

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Precise diagnosis is necessary for the treatment of the pneumonias. The introduction of the sulfonamide drugs has proven a very great advance. These drugs are bactericidal and bacteriostatic for pneumococci (regardless of the chemical composition of the capsular carbohydrate which characterizes the individual types), for some varieties of streptococci and for other organisms. The several drugs of this group are not equally effective against all these bacteria. Moreover, the sulfonamide drugs are not effective against some organisms responsible for consolidation of the lung, so that the etiology of a consolidation must be determined to prevent the administration of an often disagreeable and sometimes dangerous drug, and to permit the application of other available specific therapy where indicated.

An adequate examination for determining the etiology of a consolidation may require repeated examinations of the sputum with inoculation of mice, an examination of the blood and of the urine for organisms and for their specific products of metabolism, and the blood and tissues for specific substances (antibodies) produced by the patient. Even after the administration of sulfapyridine, pneumococci may be present in the sputum, especially in the patients who have abundant organisms and those who are not responding to the drug. It may happen that the organisms are present but do not grow readily because of the presence of drug in the sputum, and that they will appear on culture after dilution or on mouse passage. It is preferable to examine the sputum for organisms before these drugs are administered, but the prior administration of the drug is no excuse for failure to examine the sputum should a favorable response be delayed or absent. When no pneumococci are found after such careful examinations, the responsibility of pneumococci may be tentatively excluded especially if the clinical course suggests another etiology or after a twenty-four hour chemotherapeutic test without clinical effect. Pertussis pneumonias due

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to B. pertussis are not benefited by sulfonamide drugs. Pneumococci are present and responsible for the pulmonary consolidation in more than 10 per cent of patients suffering from pertussis. These latter patients have pneumonias of pneumococcic origin accompanying their pertussis and are benefited by specific chemo or serum therapy.

A blood culture is always necessary in patients suffering from pneumonia because a bacteremia may exist and the etiology of the pneumonia may be thus determined when sputum examinations have not revealed pneumococci or a pneumococcus is found which was merely carried by the patient. However, the pneumococci which are found in the sputum in the presence of a consolidation are responsible for the pneumonias in 93 per cent of cases. If there is doubt as to their connection with the disease or if there is an infection of the upper respiratory passages, secretion should then be obtained directly from the lung by laryngoscopy or by transthoracic aspiration. The urine rarely contains pneumococci, but the urine may be concentrated and tested for the presence of specific soluble substance produced by the invading pneumococcus. For this test the urine is concentrated ten times and a precipitation test with suitable controls is performed using specific antibodies. The organism when found in the blood or its metabolites, when present in the blood or urine, should be regarded as the cause of the existing pneumonia. We have found pneumonia due to a pneumococcus recovered from the sputum and a concomitant bacteremia due to a different pneumococcus or another organism unrelated to the pneumococcus.

Pneumococci vary in their tendency to attack the lungs and invade the blood. Patients vary in their ability to resist the organisms. Because of the difference in the habits of the organisms in respect to site of invasion, age, and sex incidence, physicians may be guided in prognosis and therapy. A knowledge of the type and the habits of the pneumococcus with which one deals aids in the interpretation of the symptoms as they arise. Pneumococcus I and pneumococcus XVIII are frequently the cause of empyema. Pneumococcus II often invades the blood. Pneumococcus III is frequently the cause of pneumonias in the aged and of otitic infections and meningitis. Pneumococcus XXIII frequently occurs in the nasal sinuses and may be responsible for meningitis. The prognosis of pneumococcic pneumonias varies with the type of pneumococcus involved.

Physicians cannot rely completely upon the bacteriostatic and bactericidal properties of chemotherapeutic agents because the vulnerability of the organisms to such agents is not known. Pneumococci may become fast to sulfapyridine and this fastness may be retained by them after passage to another patient. Fastness may be acquired in a few days. Such sulfapyridine fast pneumococci are susceptible to serum because it neutralizes their capsular substance and sensitizes them for phagocytosis.

It has been shown in infected explants of bone marrow that specific

serum augments the action of sulfapyridine (1). Humoral immunity determines the outcome of therapy in many patients, either by acting as an adjuvant to serum therapy and chemotherapy or independently.

Among 65 patients treated with sulfapyridine and studied at frequent intervals for the presence of antibodies, it was found that all those who developed sufficient antibodies so that agglutinins and precipitins could be demonstrated, recovered, and that deaths occurred among those who had either a lower titer of antibodies (agglutinins only) or no measurable immune response at all. Unless he knows the etiological agent involved, the physician cannot study the immunological response or properly select chemotherapeutic agents. Sulfapyridine is effective against pneumococci and streptococci and sulfathiazole, against these organisms as well as staphylococci. Without knowledge of the specific type of pneumococcus or streptococcus, he is unable to use serum therapy even if it is indicated, because it requires "type" diagnosis. It is only by precise knowledge of the etiology in respect to type of organism, that the presence of antibody or specific soluble substance may be known. If a patient has soluble carbohydrate in the blood the prognosis is three times as bad as when there is a bacteremia without circulating specific carbohydrate, and more than twenty times worse than when there is neither bacteremia nor circulating carbohydrate (2). Patients with pneumococcus I rarely have circulating carbohydrate in the blood. In none of 32 patients who were examined frequently for this substance, was it found. It is present in one-third of the patients with pneumococcus III pneumonia; in one-eighth of the pneumococcus VII pneumonias; one-tenth of the pneumococcus VIII pneumonias; in many B Friedlander A pneumonias, and has been found in pneumonias due to other types of pneumococci. It is found especially in those patients who are severely stricken. It may appear in patients who are doing poorly under treatment when it had been previously absent. It is a product of bacterial metabolism and the drugs which depress bacterial growth reduce its production. Although chemotherapy does not neutralize the specific carbohydrate already formed, the specific carbohydrate may disappear from the blood of some patients if its further production is stopped by chemotherapy. The continued presence of specific soluble substance in the blood means continued infection, even though the temperature may have fallen to nearly normal. Usually in such patients the pulse continues to be rapid.

The specific carbohydrate (specific soluble substance) is neutralized by autogenous antibody or by antibodies introduced in therapy. When antibody is present, the prognosis is better. Soluble carbohydrate may be detected, either by properly controlled precipitation tests, or by the reaction with intradermally introduced antibody. Conversely, antibody may be detected by properly controlled precipitation tests or introduction of soluble carbohydrate. Care, however, must be taken to avoid non-

specific skin reactions. It is impossible to determine the presence of either carbohydrate or antibody unless the specific organism responsible for the disease is known. In our series of frequently studied patients who received sulfapyridine, all recovered when autogenous antibodies were found in the blood before the eighth day. The outcome was not as favorable when antibodies were introduced. This may be due either to a difference in the antibodies or to a failure of sufficient tissue reaction. Some patients who had no demonstrable antibodies recovered. Only if the type of pneumococcus is known can this problem be clarified.

In very ill patients one must not rely solely on depression of the invading organism's growth by sulfapyridine because a sulfapyridine-inhibiting substance may be formed in the tissues or be released by autolyzing organisms. It has been suggested that *p*-aminobenzoic acid is one of the sulfapyridine-inhibiting substances. Sulfapyridine depresses the metabolism of the organism it affects. In some cases it actually destroys it completely. However, a few organisms may survive and if the defenses of the body are inactive or inadequate, the surviving organisms may be stimulated to renewed and overwhelming growth by auxins. The latter may come either from the tissues, or from autolysis of bacteria. The ancient principle of medicine, "*ubi pus ibi evacuo*" is especially applicable during chemotherapy because sulfapyridine antagonists and auxins may develop or be liberated from purulent foci.

Chemotherapy of the pneumonias is not used to augment the natural defenses but to depress the vitality of the invaders. If the defenses are adequate, chemotherapy or depression of the invaders may be ample; after it is employed, the pulse and temperature promptly return to normal. When it is insufficient or there is no auxiliary humoral response, augmented growth of the pneumococci may take place and the patient relapses. Further chemotherapy may be used in the hope that the humoral defense will meanwhile have become sufficiently strong. When there is a severe infection, natural resistance, if it is weak or tardy, may become exhausted so that specific carbohydrate accumulates in the blood. In such patients the natural defenses may be augmented by neutralizing the carbohydrate with therapeutic serum. It is well known that soluble carbohydrate depresses phagocytosis in pneumococcic infections.

It is probable that we shall ultimately conclude that there is an appropriate method of therapy for each patient and we shall be able to select it in the light of what can be determined by suitable tests. Treatment may be either a single agent or a combination of remedies. If the physician knows his patient's response to therapy, he may chart the course of the pneumonia which should be short if appropriate remedies are chosen. It may be long and stormy, if the patient comes for treatment late, and with many invaders aboard who have been given confidence by inadequate or delayed counter-attack.

The temperature may continue to be elevated after chemotherapy. This may be due to continued infection as a result of an insufficient concentration of the chemotherapeutic agent; the concentration may be inadequate because of poor absorption of the drug; because there is a very large number of organisms; or because the drug is inhibited. In any case, the action of the drug may be augmented *by* strengthening the resistance of the host *by* neutralizing the circulating carbohydrate and rapidly providing antibody through the administration of serum. If antibody is already detectable in ample amount, it is useless to continue administration of the serum. In that case, the antibody may have been incomplete or unsuitable because of errors in typing or in the collection of the material, or, there may be additional, different invaders. It may be wise then, to add chemotherapy while the patient is restudied. An organism differing from the original invader and insusceptible to the chemotherapy may have entered the picture but without previous exact bacteriological etiological study this cannot be verified. Even when there is an effective concentration of the drug in the blood, the temperature may continue to be elevated. In such a case, the organisms may not have become fast to the drug; there may be ample immunity response, and the blood may have been made bactericidal for the incitant of the consolidation. The drug itself may be responsible for the temperature elevation and, if continued, may produce shock and death of the patient. Under these circumstances, knowledge of the type of pneumococcus is essential and we can only act with assurance if we know the state of the patient in respect to immunity.

The difficulties of deciding on the best remedy in the pneumococcic pneumonias is shown by a glance at the following summary of statistics. Elsewhere (3, 4) we have discussed the errors in the interpretation of such summaries when age of the patient, day of the disease, concomitant

Adult Statistics—Pneumococcic Pneumonias

PERIOD	SERUM			CHEMOTHERAPY			SERUM AND CHEMOTHERAPY		
	Cases	Deaths	Per cent	Cases	Deaths	Per cent	Cases	Deaths	Per cent
1938–39	256	36	14.1	165	16	9.7	171	29	17.0
	41*	16*	39.0*	16*	7*	44.0*	27*	11*	30.8*
1939–40	117	9	7.7	358	48	13.4	196	25	12.8
	20*	4*	20.0*	31*	10*	32.2*	24	10*	41.7*
Total 1938–40	373	45	12.1	523	64	12.3	367	54	14.7
	61*	20*	32.8*	47*	17*	36.2*	51*	21*	41.2*
Bacteremic incidence		16.3%			9%			13.9%	

* Bacteremia.

pathology, bacteremia and, more recently, the presence of specific soluble substance, are not taken into account. Many more carefully controlled observations, in which these factors are considered will have to be made.

It seems, from what has been said, that intelligent care of a patient with pneumonia requires precise knowledge of the etiology (including the immunological type) if one is to select the appropriate remedy and to meet complications which may arise in the course of the disease either from the organisms involved or from the treatment employed. Typing is of practical value because it permits the physician to select the appropriate treatment for each patient and assists him to interpret the clinical status of the patient who is to be conducted through a dangerous illness.

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MEDIASTINITIS FOLLOWING ESOPHAGEAL PERFORATION BY INGESTED BONE

Cervical Mediastinotomy with Subsequent Absorption of Foreign Body

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Perforation of the esophagus by a foreign body with accompanying mediastinitis is serious. The varying degrees of the clinical picture, the clinical findings and complications and the judgment in choosing the best type of therapy have engaged the attention of surgeons and esophagoscopists for many years. At one time some writers considered the prognosis in esophageal perforation to be fatal. In recent years better coöperation between specialists, better understanding of the involved anatomical structures, better judgment and improved technical procedures have reduced the mortality considerably.

A careful study of the anatomy of the mediastinum has been made in this country (Lambert and Berry (1), Furstenberg and Yglesias (2), Coller and Yglesias (3), Phillips (4), Pearse (5, 6)). Spread of infection into and within the constantly moving mediastinum occurs along fascial spaces, such as the previsceral, pretracheal, retrovisceral and the carotid sheath. The retrovisceral space is the most frequently involved; it extends in front of the prevertebral fascia from the base of the skull to the diaphragm (Jemerin and Neuhof (7)) and laterally to the carotid sheath. This space presents two points of constriction: 1) the superior aperture of the thorax, especially where the parietal pleura is attached to the first rib on the left side, 2) that point in the mediastinum where the roots of the lungs and the great vessels are located.

The most frequent site of perforation of the esophagus is in its cervical portion. Such a perforation may be produced by organic or inorganic foreign bodies of various sizes, shapes and consistencies, and by necrosis of esophageal new-growths, by instrumentation and by non-perforative trauma to the esophagus. (Jermerin and Coleman (8)).

Neuhof (9), reporting on 60 cases of mediastinal infection, has divided them into: 1) mediastinal abscess; 2) phlegmonous mediastinitis. This is usually complicated by bilateral suppurative pleuritis.

Some authors have favored conservative therapy of mediastinitis in selected cases. Myerson (10) reports a series of twelve cases due to perforation of the esophagus and in two of these with severe constitutional

symptoms and local signs there were recoveries without operation. Keefer (11) and Head (12) have had similar cases. It has been the experience of most men that early operative intervention gives the best results and in many instances it prevents mortality. (Pearse and Heatly (13), Pearse (14, 5), Neuhof (9), Guns (15), Head (12), Phillips (4), Hunt (16)).

Two anatomical approaches to the mediastinum have been advocated: 1) cervical mediastinotomy and; 2) posterior mediastinotomy. Cervical approaches were made by von Hacker (17) in 1901 and by Marschik and Voge (18) in 1909. These were characterized by large dissections. A typical anatomical approach will be described in reporting the case in this article. Lilienthal (19) favored an approach by extrapleural posterior mediastinotomy, with resection of as many ribs as necessary.

The case reported herein illustrates the following features:

1. Perforation of the cervical esophagus by a fragment of lamb-chop bone.
2. Roentgen visualization of the foreign body with and without barium.
3. Roentgen visualization of air in the periesophageal tissue (Minnigerode sign (20)), with a barium defect in the esophagus and widening of the prevertebral tissues.
4. Failure to visualize the bone by esophagoscopy. The bone had apparently found its way into the periesophageal tissue, leaving a necrotic perforation in the esophagus.
5. Complicating mediastinitis.
6. Cure of the mediastinitis by cervical mediastinotomy; the foreign body not being located.
7. Spontaneous absorption of the bone in about twenty-four days after operation.
8. Twenty-six months of follow-up observation showing partial stricture of the cervical esophagus with its attendant symptoms.

CASE REPORT

History. A 53 year old Irish-American plasterer came to the Emergency Room of the Hospital for Joint Diseases on May 16, 1938. He had been eating a lamb-chop about 15 minutes previously and had accidently swallowed a piece of the chop bone. He complained of pain on swallowing, and pain in the region of the neck and larynx. The foreign body could not be seen by direct examination. The next day, May 17, he was admitted to the Bronchoscopic Service of Dr. M. Joseph Mandlebaum.

Examination. He was a well-developed man, lying quietly in bed and in mild distress. He had pain on swallowing. The pharynx was congested but there was no evidence of abrasion. The routine examination was irrelevant. The blood pressure was 120 systolic, 74 diastolic.

Laboratory Data. The urine examination was negative and the blood count was red blood cells 5,400,000; white blood cells, 16,300 (86 per cent polymorphonuclear cells, 14 per cent lymphocytes). The sedimentation rate was 68 min. A blood culture and Wassermann test were negative. His temperature was 101°F.; pulse rate, 88 per minute, and respirations, 20 per minute.

Course. X-ray examination (May 19, 1938) of the region of the pharynx and cervical esophagus in the right and left oblique positions was unsatisfactory.

An attempt at esophagoscopy (May 21, 1938) failed because the patient did not cooperate.

A lateral roentgenogram (May 23, 1938) of the cervical region (Fig. 1) revealed an opaque foreign body, about 2.5 cm. long, vertically directed and apparently in the soft tissues between the trachea and esophagus. The upper border of the foreign body was at the upper level of the second dorsal vertebra. The irregular areas of contrast sub-

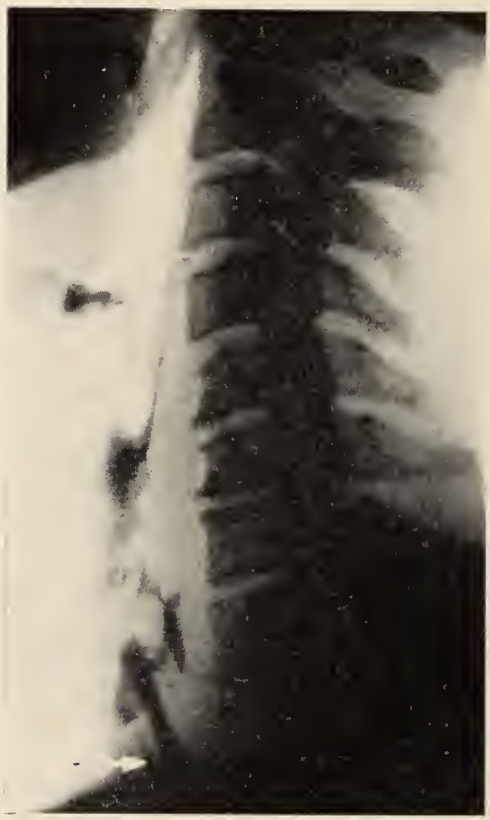

FIG. 1. Preoperative visualization of the foreign body shown by arrow. Note the accompanying barium-filled cavities and the widening of the prevertebral tissues which show interstitial emphysema.

stance represented swallowed barium, some of which was extra-esophageal. There was also widening of the prevertebral area with interstitial emphysema in this area.

Esophagoscopy by Dr. Mandlebaum showed a ragged necrotic perforation of the posterior wall of the esophagus in the subcricoid region. The foreign body could not be seen or touched with a probe. There was no free pus. The diagnosis was: "Perforation of the cervical esophagus; mediastinitis; extra-esophageal foreign body."

The bronchoscopic service attempted an approach to the mediastinum by a suprasternal incision under novocaine local anesthesia. This was not successful. Gas and a serous fluid escaped from the wound.

For the next twelve days the patient was treated by dressings, sulphanilamide and sedatives. He was allowed to swallow fluids and he also received glucose solution intravenously. His temperature ranged between 99°F. and 100.5°F. except on May 28, when he had a chill and a temperature of 103°F.

When consulted on June 4, 1938 I advised immediate surgical intervention in view of the progression of the symptoms. Three days later the patient was operated upon.

Operation (June 7, 1938) (Dr. Louis Carp). Left cervical mediastinotomy and drainage for abscess of posterior superior mediastinum, under avertin, gas and oxygen and ether anesthesia. An esophageal bougie was passed into the esophagus through an esophagoscope by Dr. Mandlebaum. An incision 8 cm. in length, was made over the anterior border of the left sternomastoid into the inferior cervical triangle. The skin,

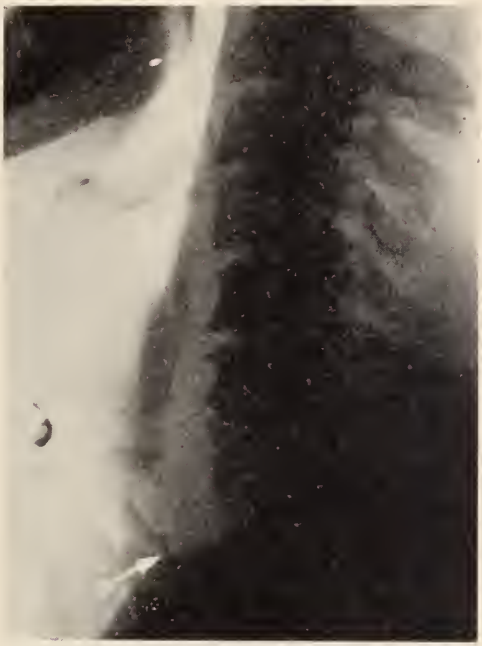

FIG. 2. Eighth day postoperatively. The foreign body has been partially absorbed. There is widening of the prevertebral area with some air around the foreign body.

superficial fascia, platysma and deep fascia were divided. The sternomastoid muscle was retracted laterally and the sternohyoid and sternothyroid muscles were retracted mesially. The internal jugular vein presented itself very prominently and was about the size of an adult thumb. This was probably produced by increased venous pressure due to the type of respiration and the presence of the esophageal bougie. The omohyoid muscle was retracted downward, the inferior thyroid vessels were ligated and cut, and the thyroid gland was retracted mesially. The trachea was identified and the esophagus behind it, and the postero-superior mediastinum was gradually entered behind the esophagus by blunt and sharp dissection. There was a sudden gush of sanguinopurulent fluid. The foreign body could not be felt. It might have been between the trachea and esophagus. Because of the poor condition of the patient it was thought advisable to terminate the operation as quickly as possible.

The mediastinum was drained by rubber dam and gauze. A culture of the pus showed facultative streptococcus hemolyticus and non-hemolyticus and a diphtheroid bacillus.

Postoperative Course. Immediately after operation the patient was placed in an oxygen tent because of his extreme cyanosis. On the first day he was in comparatively good condition. The temperature was 100°F, pulse rate, 100 per minute; and respirations, 24 per minute. He received a venoclysis of 5 per cent glucose solution and his urinary output was adequate. He was kept in the oxygen tent for two days and subsequently he was permitted to have water by mouth in teaspoonful doses. The fluids by mouth were gradually increased. On the fourth and fifth days

FIG. 3. Ten and a half months postoperatively. Note constriction of esophagus n operated area.

his temperature rose to 103°F. On the fifth day he was taking ice cream, on the sixth day, cereals, custard, milk and cream and on the seventh day a semi-soft diet.

The Wound. This had a profuse foul discharge. On the eighth post-operative day, a redressment was done in the operating room. The packing and rubber dam were removed from the mediastinum. There was retention of a profuse amount of foul pus. This was aspirated. A soft rubber tube was inserted into the mediastinum which was subsequently irrigated through the tube with aqueous azochloramide solution. On the sixteenth postoperative day the discharge was less foul and much diminished. The patient had much less pain on swallowing as compared to his preoperative pain. On the twenty-sixth postoperative day there was practically

no drainage and the wound was almost closed. He was discharged on the twenty-seventh postoperative day to the Out-Patient Department. The wound was completely closed on the fifty-third postoperative day.

Postoperative Roentgenograms of the Foreign Body. First Day. The linear opaque shadow representing the foreign body was present anterior to the body of the first dorsal segment. There was widening of the prevertebral soft tissues in this area, with some air around the foreign body.

Eighth Day. The foreign body was still present but much thinner (Fig. 2). There was persistent widening of the prevertebral area with some air around the foreign body.

Seventeenth Day. The foreign body was not clearly outlined and there seemed to be partial absorption.

Twenty-fourth Day. There was no evidence of the foreign body.

Follow-up Result. During the first six months the patient had no complaints. At the end of nine months the patient complained of a choking sensation in operative area, with some dysphagia and dyspnea. A gurgling sound could be heard when he swallowed. At the end of ten and a half months dysphagia persisted and a barium roentgenogram (Fig. 3) of the esophagus showed adhesions and constrictions of the esophagus at the level of the first dorsal vertebra, with dilatation proximal to it. At the end of eighteen months the patient complained of dysphagia. Twenty-six months later there is pain on swallowing; the patient eats small amounts of food of a semi-soft consistency. There is occasional temporary esophageal obstruction, with gurgling on swallowing. The left cervical scar is 7.5 cm. in length and is well healed.

SUMMARY

A 53 year old male had a perforation of the cervical esophagus due to a piece of ingested lamb-chop bone. This could not be located by the esophagoscopist. Roentgenograms with the aid of barium showed it to be in the region of the cervical esophagus, with an accompanying barium defect in the esophagus, air in the periesophageal tissues and widening of the prevertebral space. After a latent period of twenty-one days, a cervical mediastinotomy was performed, with recovery and postoperative absorption of the bone. A twenty-six months' follow-up result showed a constriction of the esophagus in the operative area with attendant symptoms of dysphagia and pain.

A brief review of the literature is given. Early operative intervention in mediastinitis due to esophageal perforation is advocated.

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MULTIPLE CALCIFIED INTRAVENTRICULAR MENINGIOMAS

Case Report

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Single meningiomas lying entirely within one of the ventricular cavities constitute a very small percentage of the total of intracranial meningiomas. Some of these intraventricular tumors are densely calcified but the majority of them are not. Multiple intraventricular meningiomas are exceedingly rare. In his monograph on meningiomas, Cushing (3) describes a patient from whom, in addition to meningiomas of the convexity, he removed similar calcified tumors from the right lateral and third ventricles. In this same chapter he details another instance of such a tumor in the left lateral ventricle. He refers to the case of Christophe and to seventeen additional instances of intraventricular meningiomas, many of which were unpublished. Additional case reports of unilateral lesions are those of Gardner and Turner—3 cases (7), Gross (8), David, Guillaumat and Askenasy (4), Busch—5 cases (1), DeBusscher (5), Roscher (10), Ferraro and Siris (6), Jefferson and Jackson—3 cases (9) and Campbell and Whitfield (2). The only instance with bilateral calcified tumors is an unoperated case of Cairns to which Cushing refers. The diagnosis confirmed at autopsy was made before death and based on the calcifications shown by x-ray. The total number of reported intraventricular tumors is about forty.

A case with multiple calcified intraventricular meningiomas is herewith detailed.

CASE REPORT

History. (Adm. 419212.) F. S., a thirty-eight year old female presented x-ray evidence of intraventricular tumors. A meningioma was removed from the left ventricle. Shadows were seen remaining in the right lateral and third ventricles, however, further surgery was refused.

In January 1938, a thirty-eight year old, unmarried woman was admitted to the hospital because of headaches of somewhat over one years' duration. These were generalized and constricting in character, aggravated by straining and somewhat relieved on lying down. Of more recent onset, was blurring of vision, which interfered with reading. A sister had noted that for two years the patient had been less sociable and that she often repeated phrases. One and a half years prior to her admission a cholecystectomy and appendectomy had been carried out without complications. Because of the headaches, an x-ray examination of the skull was performed and showed calcification. Because of this, she was referred to the hospital rather than because she felt ill.

Examination. The patient displayed coarse hair with masculine distribution. She was talkative, flippant and euphoric. There was bilateral papilledema up to one and a half diopters. The deep reflexes were all hyperactive without any differences on the two sides. The left abdominal reflexes were less active than the right.

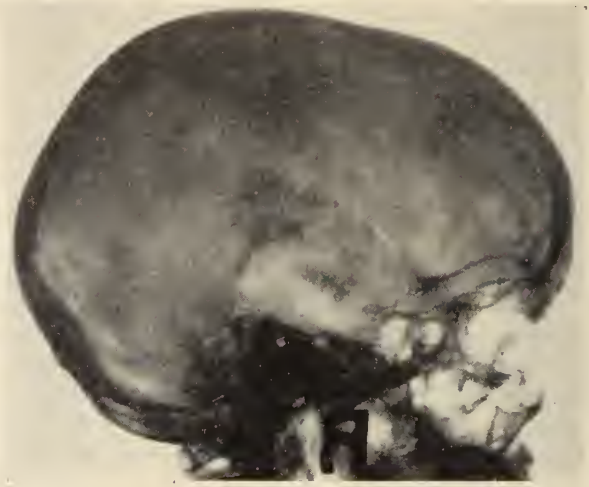

FIG. 1. Calcification in skull plate

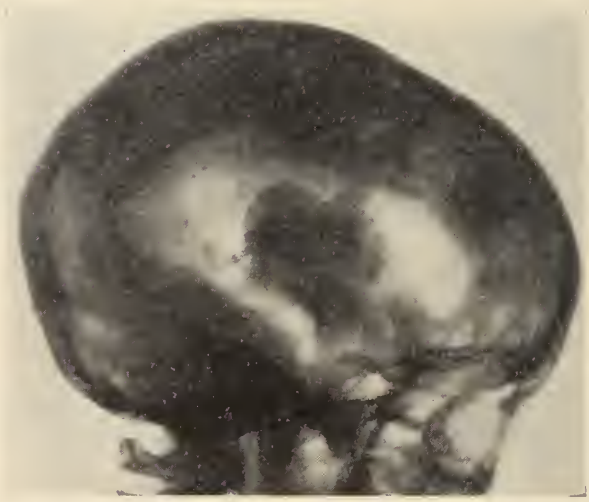

FIG. 2. Calcified mass in ventricle delineated after air injection

There were no pathological reflexes. There was no abnormality in sensation, motor power, or cranial nerves other than the eye changes noted. There was no visual field defect. Caloric responses were normal.

Laboratory Data. The spinal fluid was under a pressure of 300 mm. of water. It contained 3 cells and 43 mg. per cent of protein.

X-ray examination of the skull showed what was first taken to be a single calcified

mass, 5 cm. in diameter, situated slightly on the left side but extending across to the right. Destruction of the posterior clinoids and dorsum sellae was noted (Fig. 1).

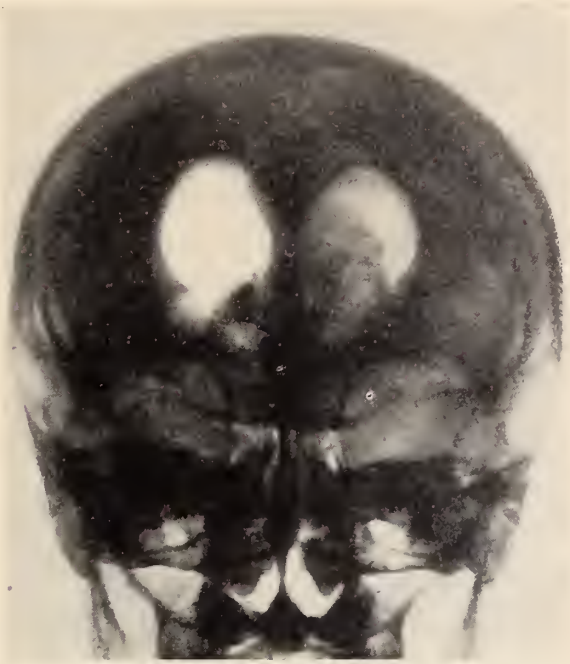

FIG. 3. Calcification in both lateral ventricles, delineated after air injection

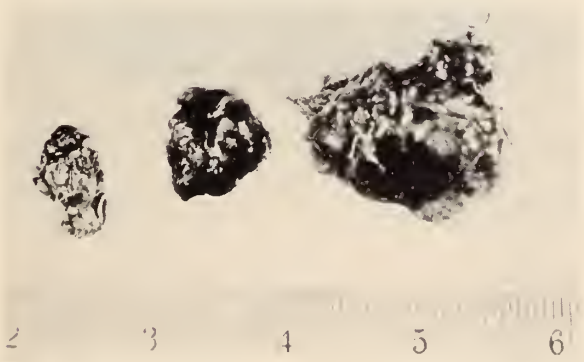

FIG. 4. The two larger pieces are tumor, the smallest choroid plexus

A ventriculogram showed a dilated ventricular system. A large calcified mass was seen in the left lateral ventricle, a smaller one in the right ventricle, and a shadow in the position of the third ventricle (Figs. 2 and 3).

Operation. The mass on the left side was larger and it was decided to remove it first. An osteoplastic flap was planned to allow incision of the cortex where the

tumor most closely approached it, namely, in the left frontal region. The cortex was incised just lateral to the midline in the premotor area and the ventricle entered. When the nodular tumor was first exposed, it was thought to spring from the mesial wall of the ventricle and to be covered with ependyma, but on manipulation, the tumor moved so freely that it was recognized as a pedunculated mass attached to the choroid plexus. The tumor was removed in two pieces and a portion of the choroid plexus was excised (Fig. 4). The entire mass weighed 33 grams. Doctor J. H. Globus reported the tumor as a meningioma and the choroid plexus as showing neoplastic islands and collections of psammoma bodies.

Course. The postoperative course was marked by a right hemiplegia and aphasia from which she was recovering at the time of her discharge from the hospital, five weeks after the operation.

When seen six months later there was a shade of right sided weakness and occasional hesitation over words. Since that time there has been further improvement

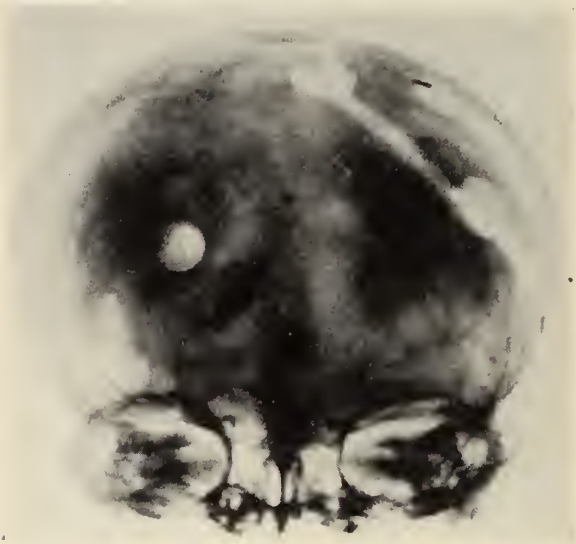

FIG. 5. Postoperative x-ray showing calcifications remaining in right lateral and third ventricles

according to letters received. It has been impossible to persuade the patient to enter the hospital for the removal of the other tumors, since she claims to be symptom-free.

COMMENT

The x-ray studies made after the removal of the tumor show shadows on the right and in the midline (Fig. 5). Whether these are two separate lesions such as described by Cushing in the "case of Edith Mindes" or a tumor of the third ventricle projecting into the lateral ventricle as described by Jefferson and Jackson, cannot be determined from the x-ray studies, although the appearance suggests separate tumors. Though there is no proof, there is every reason to believe that the remaining calcifications are in meningiomas.

Should this latter assumption be correct, the case would be unique in presenting three separate intraventricular tumors. The relative infrequency of intraventricular meningiomas may be judged by the fact that Cushing encountered but two in his 295 intracranial meningiomas. Busch, however, recorded five cases among 502 verified brain tumors of all kinds.

There is nothing characteristic about the symptomatology or physical signs in this type of tumor. Headache, which is the usual presenting symptom, may be paroxysmal. This is more apt to be so if the tumor is small and movable so that the interventricular foramen can be intermittently blocked. Mental changes are noted frequently, as is papilledema. Localizing signs, as one would expect, are absent. Accurate localization will depend upon air studies. Once localized, the fact that the sole blood supply comes from the choroid plexus makes the lesion particularly favorable for extirpation unless the extreme size adds to the surgical difficulties.

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ENDOCHOLEDOCHAL SPHINCTEROTOMY

With a Report of Four Cases

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Although Gage (7) first mentioned the sphincter of the common bile duct in cats in 1879, it was Oddi (14) who accurately described this structure both in animals and in man. These original observations were subsequently confirmed by Hendrickson (9), Helly (8) and others. This muscle, however, has more than an academic significance. It plays an important role in the sphincter mechanism. This includes, in addition to the tonus of the sphincter of Oddi, the diagonal passage of the choledochus through the duodenal wall and the tonus of the duodenal smooth muscle together with its muscularis mucosae. Collectively these structures not only resist the passage of fluid from the common bile duct into the duodenum, but prevent the reflux of duodenal contents into the choledochus. The effects of spasm of the sphincteric mechanism has been clearly demonstrated by roentgenographic studies of lipiodol injections of the choledochus together with pharmacological studies of the intraductal pressure reported kymographically according to the method of Katz (10). Physiologic disturbances of the sphincter of Oddi probably bear a most important relationship to certain types of pancreatitis, gall bladder disease, dyskinesia of the biliary tract and some forms of transient jaundice. Rost (16), Westphal (20), Liek (11) and others have felt that many of the unrelieved symptoms following cholecystectomy were often attributable to spasm of the sphincter of Oddi. It has been suggested that many of the factors responsible for this sphincter spasm may have a constitutional basis, and that some may be related to either the menstrual cycle or pregnancy, while others may be due to psychic disturbances. Cases of periodic jaundice have been reported during the menstrual cycle. Nanu-Muscel and Pavel (13) report cases in which exploratory laparotomy proved that pre-existing jaundice must have been due to a spasm of the sphincter caused by psychic trauma, as the icterus occurred after fright.

If some of these pathologic states are so intimately associated with disturbances of the sphincter mechanism, then it is extremely important that spasm of the sphincter be relieved either temporarily or permanently. Most patients with sphincter spasm respond readily to medical measures, especially those who are presumably suffering from either endocrine disturbances or inbalances of the sympathetic nervous system. Many

patients have been definitely relieved by rest, dietetic corrections and duodenal lavage with magnesium sulphate. However, these conservative measures are not always successful. The persistence of severe and distressing symptoms, especially after cholecystectomy, often call for surgical intervention. It is in those cases in which careful abdominal exploration fails to disclose any gross pathologic alterations that attention should be focused upon a dyskinesia of the sphincter of Oddi as a possible source of the symptomatology.

Several surgical methods have been advocated and employed to relieve this localized muscular spasm. Instrumental dilatation of the sphincter obtained by passing graduated sounds through the common bile duct into the duodenum is a popular method. This procedure, advocated by many, has had its complications. If the dilatation has been forceful and the sphincter mechanism has been unduly traumatized, an ascending anaerobic infection by Bacillus Welchii from the duodenum may result. Deaths have been reported from this cause. Another method advocated is that of biliary duodenal intubation. A "T" or straight rubber tube is inserted into the common bile duct, and then passed through the sphincter into the duodenum. This accomplishes practically the same result as instrumental dilatation of the sphincter. The indwelling tube insures not only the free delivery of bile into the intestine but its mechanical presence maintains a persistent dilatation of the sphincter until the rubber "T" tube is either withdrawn, or the straight tube is spontaneously eliminated through the bowel. This method which is not particularly dangerous has been advocated especially by Duvall (5) and Walzel (19). The procedure has never gained great popularity in this country.

Other European surgeons, notably Sasse (17), Floercken (6) and Peterman (15), when confronted with either a calculus inpacted at the ampulla or papillary stenosis, or when dealing with sphincter spasm, prefer a choledochoduodenostomy. The side-to-side anastomosis of the dilated common bile duct with the duodenum eliminates the sphincter mechanism and naturally short-circuits the flow of bile. This operation, in addition to its technical difficulty, however, has another disadvantage. Theoretically, an ascending infection by duodenal reflux is always a potential possibility. However, the clinical instances of this complication appears quite rare in spite of the fact that gastro-duodenal roentgenograms in these patients often demonstrate the presence of barium in the common bile duct.

It should be remembered, however, that instrumental dilatation of the sphincter and biliary duodenal intubation are only temporary measures, and that there is always the possibility that attacks of intense muscular spasm may recur. While the results of choledochoduodenostomy are more permanent, the procedure has an appreciable operative mortality and a postoperative morbidity.

However, there is another surgical method available in which the sphincter of Oddi may be attacked directly.

The musculature of the sphincter may be permanently paralyzed by actual surgical section of its fibers. Transduodenal sphincterotomy is not a new procedure, for transduodenal choledochostomy for impacted ampullary calculi has been done for years. In order to extract the impacted stones in these cases, it is necessary to divide the sphincter. This procedure *per se* has not resulted in any unusual complications. Recently, Archibald (1) has reported several cases in which he has divided the sphincter transduodenally for spasm alone, and del Valle (18) has sectioned it through the duodenum for "odditis", a condition in which a retracted sphincter partially obstructs the flow of bile. Naturally, duodenostomy may entail certain postoperative complications. Peritonitis, duodenal fistula, and physiological disturbances incident to duodenal adhesions are always possibilities. These obvious objections to transduodenal sphincter-

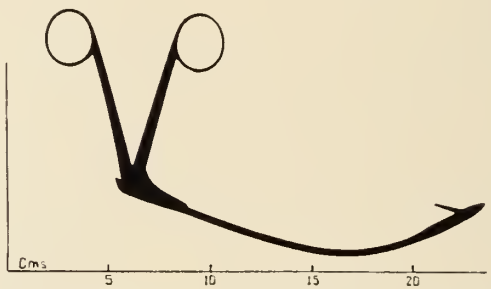

FIG. 1. The sphincterotome with knife blade open. The shaft, which is 16 centimeters long and 4 millimeters in diameter, has a flattened tip measuring 35 by 6 by 2.5 millimeters. The shearing blade which fits into a slot in the tip, has a thickness of 1.5 millimeters and an effective cutting length of 11 millimeters.

otomy may be eliminated by endocholedochal sphincterotomy. In this procedure the sphincter is divided by means of an especially designed instrument. The sphincterotome which is illustrated in Figure I is introduced, with the knife closed, through a choledochostomy into the duodenum via the sphincter. The knife is then opened and the instrument is carefully withdrawn until it is firmly impinged upon the sphincter. When the knife is closed, the sphincter is divided. The instrument is then withdrawn, often with a segment of tissue from the sphincter region, and the common bile duct is then drained with the T-tube.

The experimental results of endocholedochal sphincterotomy have been previously published. This operation, which was easily performed in a series of cholecystectomized dogs, effected a reduction in the functional efficiency of the sphincter mechanism. The procedure was not followed by any evidences of ascending infection of the biliary tract. Its safety was further demonstrated, as far as visible injury to the duodenum and

pancreas was concerned, by performing an endocholedochal sphincterotomy in a series of cadavers. It has been tried clinically in a few selected cases in which it was felt that spasm of the sphincter seemed to have played an integral part in the symptomatology which was present.

A resumé of the first case which has been previously published in detail (2) will again be given with recent follow-up reports.

CASE REPORTS

Case 1. History. (Adm. 406280). L. C., a married female, 24 years of age, was referred by Dr. I. A. Feder of Brooklyn, New York, to whom we are indebted for her history and laboratory studies. She was first admitted to the Beth El Hospital, Brooklyn, New York, on August 5, 1932. Her past history was practically negative, except that for two and a half years following her second pregnancy she had experienced attacks of right upper quadrant pain which radiated to the back and right shoulder.

The present illness began rather abruptly with high fever, chills, delirium and rigidity of the neck. The physical examination revealed findings suggestive of typhoid fever, which all laboratory data confirmed. The patient subsequently complained of severe pain in the right upper quadrant of the abdomen, and on physical examination a mass was noted in this region. There was no jaundice and the white blood count was normal. In spite of the fact that the patient was critically ill, a laparotomy was performed under spinal anesthesia on September 14, 1932.

An enormously distended, partially necrotic gall bladder, with a pericholecystic abscess completely enveloped by omentum, was found. There was a stone in the cystic duct. A cholecystostomy was performed. The patient was finally discharged in November, 1932 with a biliary fistula which eventually closed in a period of two months.

The patient then began to experience attacks of severe biliary colic which were relieved only when the fistula spontaneously reopened with the free discharge of bile and pus. Because of these repeated episodes, the patient was admitted to the Brooklyn Jewish Hospital for exploration on May 30, 1933. The operation, which was performed under spinal anesthesia, revealed a chronically inflamed gall bladder with stones in the cystic duct. The common duct was probed and found free of calculi. Following a cholecystectomy, she made an uneventful recovery and was discharged June 18, 1933.

She remained well for a short time when she began to experience episodes of pain which were described as rather characteristic. A few days previous to the onset of the attack, the patient experienced severe hunger. The pain then started in the right lower quadrant, radiating around the right side to the back, and upward to the right shoulder and arm. There was nausea, but no vomiting. The pain lasted for a short time and either terminated spontaneously or was relieved by an injection of morphine sulphate, at times three-quarters of a grain being required (nitroglycerine was without effect). After the attack subsided, there was residual tenderness in the right upper quadrant and along the course of the colon, and pruritus which was followed by a generalized urticaria. Jaundice was never noticed.

In view of the repeated attacks of pain, exploratory laparotomy was advised since it was felt that the patient was suffering either from periodic attacks of spasm of the sphincter of Oddi or possibly a common duct stone. The patient entered The Mount Sinai Hospital on March 25, 1937.

Operation. An exploratory operation was done under avertin, supplemented by gas, oxygen and ether anesthesia, on March 26, 1937. The liver and gall bladder bed

appeared normal. There was no evidence of a cystic duct. The common bile duct which was normal throughout its course, did not appear dilated, and on aspiration was found to contain clear, golden-yellow bile. The stomach, duodenum and pancreas, which were clearly visualized, were normal. The uterus was retroverted, but normal in size and shape. The adnexa felt normal. There were many intra-peritoneal adhesions which were divided in order to expose the common bile duct adequately. By means of the Hoffman punch a biopsy specimen was taken from the liver and pancreas. (These were subsequently reported as showing no significant changes). The common bile duct was incised between Allis clamps and probed without difficulty; it did not contain any calculi. A sphincterotomy was performed. The sphincterotome was introduced into the common bile duct and through the sphincter into the duodenum. The knife was opened and the instrument withdrawn until it firmly infringed upon the sphincter. The knife was closed, thus dividing the sphincter without difficulty. The instrument was withdrawn, and the piece of tissue which had been punched out was removed from beneath the blade and sent to the pathological laboratory for study. A T-tube was inserted into the common bile duct which was sutured about the tube with four interrupted chromic sutures. Two rubber dam drains were placed into the region of the common duct, one above, and one below the tube. The abdomen was closed in layers using chromic catgut throughout, with silk and pincettes for the skin.

Postoperative Course. There was an immediate postoperative rise of temperature to 103°F. This gradually fell to normal on the fifth day. There was free drainage of bile through the choledochostomy tube on the second day, at which time the return from an enema revealed a normal stool containing abundant bile. Lipiodol studies and manometric studies were made on the tenth and eleventh days after operation. A reduction in the sphincter mechanism was quite apparent. The T-tube which was removed on the twelfth day was not followed by any further discharge of bile. The patient was discharged on April 11, 1937, the sixteenth postoperative day.

Follow-up. This patient was last seen in June 1940, at which time she was in excellent health. Over three years have passed since the sphincterotomy. She has had no further recurrences of the attacks resembling biliary colic, nor has she had any symptoms which might be ascribed either to a stenosis of the papilla, or to an ascending infection of the duodenum.

Case 2. History (Adm. 422731), J. R., a 66 year old female was referred by Dr. H. Zazeela. Many years ago she was informed that she had gall bladder disease. However, she was symptom-free up to about six years ago when she began to complain of right upper quadrant pain from time to time. She was seen in The Mount Sinai Hospital Consultation Service in 1936, where a diagnosis of cholelithiasis and chronic cholecystitis was made following x-ray studies. These revealed a faint filling of an enlarged viscus, and on several of the films large translucent shadows were seen which were interpreted as gall stones. Incidentally, the electrocardiogram suggested myocardial involvement probably due to coronary arteriosclerosis. A moderate hypertension was also present, 200 systolic and 100 diastolic.

Following the above examination, the attacks of upper abdominal pain became increasingly frequent and more severe, the pain being relieved only by hypodermic medication of morphine. Finally, these attacks became associated with jaundice and the patient was admitted to the Semi-Private Pavilion in July, 1937. At this time she had fever up to 102°F. The icteric index was 35. There was tenderness in the right upper quadrant. The tenderness and jaundice receded after a few days and a cholecystectomy was done on August 3, 1937. The gall bladder contained many small stones. The common duct appeared patent and free of stones. The

patient made a fairly smooth recovery and was well for about seven or eight months when she again began to have attacks of upper abdominal pain, usually located in the right upper quadrant and always radiating down to the back. Again these became increasingly severe, and at times would not yield to either nitroglycerine, or morphine or papaverin.

The patient was re-admitted to the Semi-Private Pavilion in April, 1938, after she experienced an episode of jaundice and a shaking chill. The diagnosis was common duct obstruction presumably due to stones.

Operation. After several days of preparation she was explored through an upper right rectus incision, under gas and ether anaesthesia. The scar of the old abdominal incision was freed and the omentum dissected from the anterior abdominal wall. The liver was adherent to the transverse colon. There was a small portion of the stump of the gall bladder remaining. This was adherent to the common bile duct which was markedly dilated and thickened, being 1.5 cm. in diameter and lying just posterior and to the left of the stump of the cystic duct. The stump of the cystic duct was excised. The common duct was opened and a probe passed into the duodenum. No obstruction was found. The sphincter of Oddi was divided, using the sphincterotome. A T-tube was inserted into the common duct and a rubber dam drain placed in Morrison's pouch and another to the left of this area. The abdomen was closed in layers, using chromic catgut throughout and pincettes for the skin.

Postoperative Course. The patient made an uneventful recovery, except for a brief chill and rise of temperature following the removal of the T-tube. She was discharged on May 13, 1938.

Follow-up. When last seen by her family physician sometime in June, the patient was perfectly well and had no complaints. It is now two and a half years after the operation and she has had no recurrence of jaundice, chills or fever.

Comment. This case is of unusual interest. The attacks following the cholecystectomy were characteristic of a Charcot syndrome and the intermittent attacks of jaundice were thought to be due, most likely, to common duct stones. Exploration did reveal a large common duct which was thickened and filled with debris, but no actual calculi were visualized. It was felt that the non-calculus cholangitis was secondary to periodic attacks of sphincter spasm, and the sphincter of Oddi was, therefore, sectioned. This procedure was followed by freedom of symptoms and when recently seen by her family physician, the patient was in excellent health.

Case 3. History, (Adm. 457179). A 55 year old physician, referred by Dr. J. Diamond, gave a one year history of right upper abdominal pain radiating to the left shoulder. He had had three very severe attacks during this time and several lesser attacks. On two occasions there was a chill and rise of temperature and jaundice which lasted a few days. Two gall bladder x-ray series were taken, one seven months prior to admission and one a week before admission, which demonstrated a normal gall bladder both as to visualization and emptying. The past history included an episode of diverticulitis of the sigmoid two years ago and several attacks of bronchial asthma.

Examination. The patient was a thin adult male with a normal heart and lungs. Slight right upper quadrant abdominal tenderness was elicited. There was no evidence of jaundice. The hemoglobin on admission was 95 per cent with 5,700,000 red blood cells; 6,700 white blood cells count, with a normal differential count. The blood pressure was 150 systolic and 70 diastolic. The urine examination revealed the presence of a faint trace of albumin. The icteric index was 9.

Operation. On May 24, 1940, operation was performed under avertin and ethylene anesthesia, through an oblique upper right rectus muscle splitting incision. The gall bladder contained no stones. Its wall was moderately thickened, and its mucosa

gave evidence of cholesterosis. No stones were found on probing the common duct, which was dilated. A retrograde cholecystectomy was performed. The common duct, which was then probed to the ampulla of Vater, was found to be free of stones. A sphincterotome was inserted into the duodenum and drawn back firmly and a deep bite taken in the sphincter of Oddi, the specimen of which was sent to the laboratory. A T-tube was inserted into the common bile duct and fixed with chromic sutures and two rubber dam drains were inserted into Morrison's pouch. Cultures were obtained from the gall bladder bile and common duct bile. The wound was closed in layers using silk technique. Clips were used for the skin.

Postoperative Course. The postoperative course was uncomplicated, except for a short period during which the patient reacted poorly to the avertin anesthesia. Postoperative choledochograms showed no evidence of obstruction in the common bile duct and lipiodol entered the small bowel freely. Manometric studies showed a reduction in the efficiency of the sphincter mechanism.

The pathological report of the tissue obtained in the sphincterotome at the time of operation showed evidence of choledochal mucous membrane. The common bile duct was allowed to drain for a considerable period before the T-tube was removed. Following the removal of the tube the patient showed no evidence of jaundice, temperature rise or pain. The biliary drainage lasted only a brief period and then stopped entirely.

Comment. Case 3 is rather typical of a patient suffering from a non-calculus cholecystitis and cholangitis. There were definite attacks of gall bladder colic with episodes of chills, fever and jaundice. Yet the gall bladder visualized and emptied normally by the Graham test on two separate occasions.

Operation disclosed a cholesterosis of the gall bladder and some dilatation of the common bile duct. It seems logical to assume that the intensity of the attacks and the episodes of jaundice were probably caused by a spasm of the sphincter of Oddi. Endocholedochal sphincterotomy was performed. The convalescence was uneventful. It is too early in this case to evaluate the eventual results of this procedure.

Case 4. History (Adm. 458204). A. W., a 32 year old American-born housewife, was admitted June 17, 1940. She stated that for eight months prior to admission, she had experienced intermittent attacks of pain in the right upper quadrant, radiating to the epigastrium, back, right shoulder and right arm. These attacks, which persisted for as long as ten hours, occasionally were associated with vomiting, and subsided spontaneously. A Graham test four months before admission showed the gall bladder to be of normal density and unusually small in size. There was practically no contraction after a fatty meal but no evidence of calculus. The present attack of pain was of twenty-four hours' duration and was associated for the first time with light stools, dark urine and mild icterus. There were no chills or fever.

Examination. The patient was a slightly icteric, well-developed and well-nourished female. The blood pressure was 130 systolic and 90 diastolic. The abdomen was soft, not distended, and there was moderate tenderness in the right upper quadrant.

The hemoglobin was 93 per cent; white blood cells, 9600, with 81 per cent polymorphonuclear leukocytes, 18 per cent lymphocytes, and 1 per cent monocytes. Urine: Specific gravity 1019; albumin, 0; acetone, 0; sugar, 0; bile, 3 plus; urobilin 1 plus; microscopic, negative. Stool: formed; brown; the guaic test for occult blood was negative. Wassermann reaction, negative. Blood urea-nitrogen 9 mg. per cent; sugar 75 mg. per cent; cholesterol 275 mg. per cent; cholesterol ester 190 mg. per cent; icterus index 24; prothrombin index 100 per cent. X-ray examination of the abdomen showed the kidneys to be of normal size, shape and position. There was no

evidence of an opaque calculus. There were several small concretions in the pelvis which had the appearance of phleboliths. The patient was observed in the hospital for five days during which time the temperature was normal.

Operation. Operation was performed under gas, oxygen and ether anesthesia on June 17, 1940. The gall bladder was found to be slightly thickened and whitish in appearance, and contained several small stones about one and a half millimeters in diameter. The cystic duct did not appear abnormal. The common duct was moderately dilated but did not contain any calculi, but there was marked resistance to dilators at the ampulla. The sphincterotome was then introduced through the choledochotomy incision into the duodenum and the sphincter of Oddi was divided. A small T-tube was placed in the common bile duct. The pouch of Morrison was drained and the wound closed in layers.

Postoperative Course. The patient had an uneventful postoperative convalescence. The wound healed by primary union. The daily drainage through the T-tube averaged about 100 to 150 cc. On the fourteenth postoperative day, a cholangeogram showed the common bile duct and the hepatic ducts to be of normal size and configuration. No filling defects were seen. There was no obstruction at the sphincter. Kymographic records were made of the intraductal pressure and revealed a reduction in the function of the sphincter mechanism. The T-tube was then removed on the nineteenth postoperative day, and the patient discharged two days later.

The pathologic report showed chronic and acute cholecystitis. A biopsy removed from the sphincter of Oddi showed mild chronic inflammation.

Comment. This patient gave a typical history of gall bladder colic. The gall bladder, which was visualized by the Graham test, was small and of normal density, but did not contract after a fatty meal. The gross pathology at the time of operation showed mild chronic cholecystitis and the presence of several very small calculi. Yet an episode of jaundice was present. While this may have been caused by a calculus which had passed at the time of exploration, it was felt that a spasm of the sphincter must have played some role in the symptomatology. The sphincter was, therefore, divided endocholedochally.

DISCUSSION

The sphincter of Oddi undoubtedly played a major role in the symptomatology of the clinical pictures in these four recorded cases in which endocholedochal sphincterotomy was performed. In two, which have been followed for three years and two years respectively, there has been no recurrence of the prior attacks. The third and fourth cases are too recent to evaluate the end-results as yet.

Certainly in selected cases the operation itself is not difficult and does not seem to be accompanied by risk or any undue or untoward symptoms. Whether surgical section of the sphincter permanently destroys its action, and whether the scar resulting from its section will cause a secondary contraction of the papilla with a stenosis and biliary stasis, only the subsequent course of these cases and others will tell. Many of the other involuntary sphincters in man when divided never fully regain their function, and when healing does take place, stenosis does not result. Perhaps the sphincter of the common bile duct may be placed in a similar category.

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HYPERNEPHROMA OF THE KIDNEY

With Solitary Metastasis to the Cerebellum

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Although the usual presenting symptoms of hypernephroma of the kidney are referable to the urinary tract, not infrequently, the first symptom to attract attention is not from the primary tumor itself, but that due to a distant metastasis. The following case history is of particular interest because the first sign of this disease was the removal of a metastatic tumor from the cerebellum. In the absence of other demonstrable metastases, a nephrectomy was performed six weeks later. The patient is alive now two years. She is in apparent good health without any further evidence of this disease.

CASE REPORT

History (Adm. 418684). L. A., a housewife aged 51 years, was first admitted to The Mount Sinai Hospital (the Neurological Service of Dr. Israel Strauss) on January 6, 1938. She had been well up to two months before admission, when following an upper respiratory infection of one week duration, she began to complain of severe headaches, dizziness, and unsteadiness of her legs. She was unable to walk without support, always falling to the right side. The past history was irrelevant.

Examination. The patient was well developed, obese, myopic, and mentally clear. The general physical examination was negative except for marked myopia, and beginning cataract of the left eye. Her blood pressure was 145 systolic and 78 diastolic. Her gait was flat-footed with sudden lurching to the right on attempting to walk or while sitting with eyes shut. The reflexes were normal.

Laboratory Data. Caloric tests gave normal vestibular responses. The urine and blood examinations, including the blood Wassermann test, were negative. X-ray examination of the skull and paranasal sinuses was reported as negative except for marked clouding of both antra with thickening of the lining membrane and some clouding of the ethmoids.

Course. The patient was under observation for a period of ten days during which time she failed to show any evidence of focal brain disease. She left the hospital at her own request to be observed at home. The discharge diagnosis was Psychoneurosis (?).

Second Admission. The patient was re-admitted to the Neurological Service on May 23, 1938, approximately four months after leaving the hospital, because of almost constant headaches, dizziness, and increasing unsteadiness and difficulty in walking with tendency to fall to the right. Three months before re-admission, she began to lose weight, showed evidence of increasing weakness, and had frequent vomiting spells, at times almost projectile in character. At the time of re-admission, she was completely helpless.

Examination. The patient showed marked deterioration during the four months

interval. She appeared chronically ill. The skull was diffusely tender to percussion, and the cataract was mature in the left eye. Her blood pressure was 120 systolic and 80 diastolic. Mentally, she was apathetic, indifferent, non-cooperative, and disoriented as to time. She was unable to walk without support. Her abdominal reflexes were absent and the right knee jerk and ankle jerk were increased.

Laboratory Data. The cerebrospinal fluid was clear; Pandy test four plus; cells, 2 per cu. mm. The urine and blood examinations, including the blood Wassermann, were negative. The blood urea nitrogen was 17 mg. per cent. Gastric analysis showed an anacidity.

Course. The rapid deterioration of the patient, together with increasing somnolence, gave the suspicion of the presence of a cerebral neoplasm. Because of noncooperation on the part of the patient, it was difficult to say if the lesion was primary or secondary.

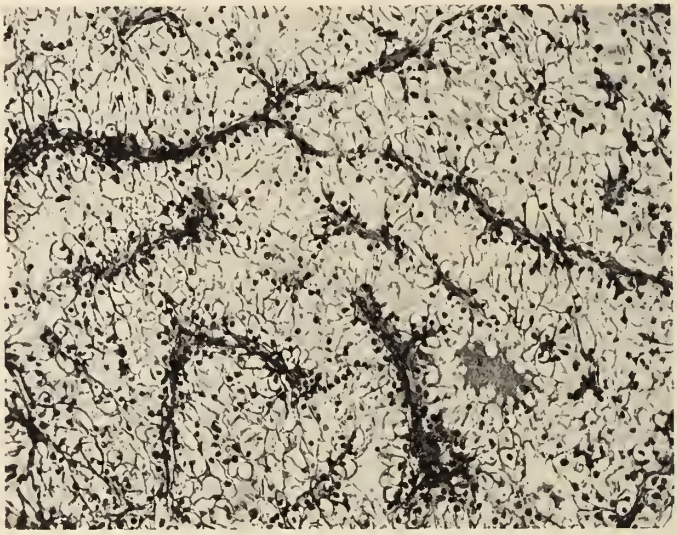

FIG. 1. Photomicrograph of tumor from cerebellum

Frontal ventriculography performed by Dr. Sidney W. Gross on June 16, 1938 was reported as showing a marked symmetrical dilatation of the lateral and third ventricles with foreshortening and dilation of the iter. The fourth ventricle was not visualized. The x-ray examination suggested a posterior fossa obstructing lesion. X-ray examination of the chest failed to show any evidence of metastases in the lungs.

Exploration of the posterior fossa was advised and a suboccipital craniotomy was performed by Dr. Ira Cohen on June 20, 1938.

Operation. (Avertin, local anaesthesia). An encapsulated tumor, 3 x 1.5 cm. in diameter, was exposed in the left cerebellum, and readily enucleated. The pathological report of the specimen was as follows: "The tumor mass measures 3 x 1.5 x 1.25 cm. Attached to it are small pieces of brain tissue intermingled with numerous areas of hemorrhage. The core of the tumor is hard. On section, the tumor appears to consist of two nodules, one being about 1 cm. in diameter and the other $1\frac{1}{2}$ cm. The nodules are white, granular, surrounded by a fairly distinct capsule and remnants of brain tissue. Each nodule contained a fairly large hemorrhagic area." Microscopic sections show the tumor to consist of large irregularly shaped cells

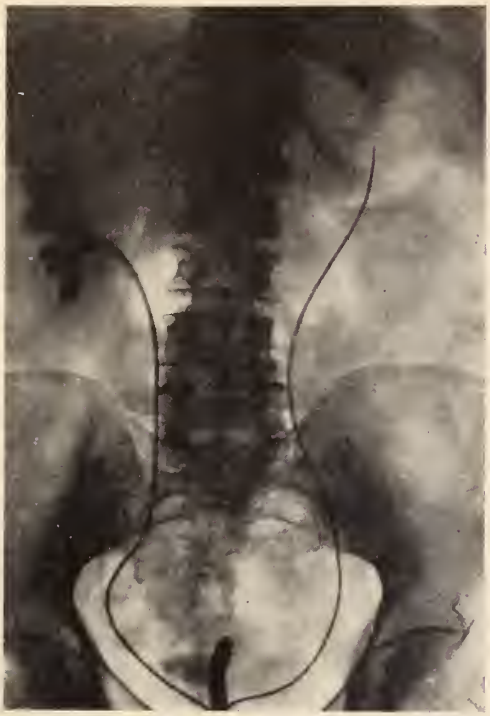

FIG. 2. Retrograde pyelogram showing deformity of superior calyx due to tumor in upper pole.

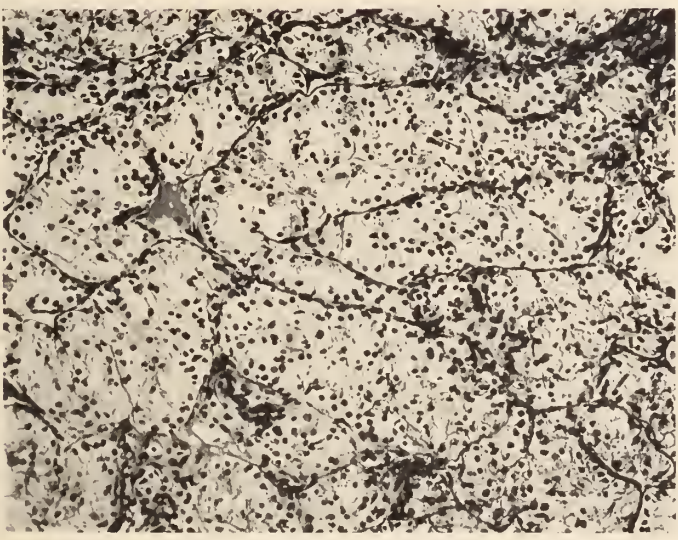

FIG. 3. Photomicrograph of tumor from kidney

with well-defined cell bodies. Most of the cells are clear, with eccentric nuclei, typical of hypernephroma (Fig. 1). Diagnosis: Metastatic hypernephroma.

Postoperative Course. The patient's convalescence following the craniotomy was uneventful, and she showed remarkable improvement mentally and physically.

An intravenous urogram taken July 6, 1938 was reported as showing a suspicious mass in the upper pole of the right kidney producing a deformity of the superior calyx with slight lateral displacement of the kidney. The left tract was normal.

The patient was seen by me in consultation on July 9, 1938, at which time an enlarged right kidney was definitely palpable. She was cystoscoped on August 1, 1938, having been ambulatory for some time, mentally alert, cooperative, and in good physical condition. The cystoscopy was negative. A retrograde pyelogram made of the right kidney was reported as showing a mass in the upper pole, compressing and displacing the superior calyx, typical of renal tumor (Fig. 2). In view of the absence of any other demonstrable metastatic foci, together with the fact that the patient made such a remarkable recovery from her brain operation, nephrectomy was advised. A right nephrectomy was performed on August 5, 1938.

Operation. (Avertin, gas-oxygen, ether anaesthesia). The kidney, harboring a tumor the size of a small grapefruit in the upper pole, was readily removed extraperitoneally through a lumbar incision. The renal vein at site of ligation did not appear to be involved.

The pathological report of the kidney specimen was as follows: "The kidney measures 15 x 9 x 5 cm. with considerable attached perineal fat together with about 15 cm. of ureter. The capsule stripped easily. Approximately the upper two-thirds of the entire kidney is replaced by a large, round, extremely cellular, hemorrhagic tumor. The tumor is fairly well localized, reaching the surface in many places, and at one point appears to be invading the capsule. The remainder of the kidney shows normal architecture. In the region of the lower pole, separate from the primary tumor, is a marble sized cortical metastasis. The renal vein is dilated and contains tumor tissue. Microscopic sections are typical of malignant Grawitz tumor, a clear cell adenocarcinoma (Fig. 3). The renal vein shows involvement."

Convalescence was uneventful. The patient was discharged from the hospital fourteen days after nephrectomy. She was referred for a course of deep x-ray therapy to the operative sites.

Follow-up. The patient has been followed for the past two years. When last seen, she had regained her normal weight, felt well, and showed no evidence of recurrence. How long this will continue, is difficult to state.

COMMENT

There is no doubt that a fairly large percentage of patients with renal tumors escape early detection not merely because of the delay in seeking medical aid, but because the presenting symptom is not due to the tumor itself, but to a metastasis or local extension. In 41 per cent of 92 cases reviewed by Creevy (5), the presenting symptoms were outside the urinary tract. The metastasis mimicked a neoplasm of the osseous system, lung and pleura, liver, brain and spinal cord, gastro-intestinal tract, female genitalia, neck and skin. In some instances the metastasis caused an unexplained anemia, unexplained fever, or simulated other disorders of the urinary tract. The first clinical evidence of renal tumor leading to a urological work-up was revealed by metastases to the lungs or bones, in 22 cases (17 per cent) out of 130 reported by Soloway (12). Hinman (6), in an analysis of 1000 cases collected from authoritative sources, found that

an early diagnosis was missed in over 90 per cent. The reason for this difficulty is the fact that hypernephromata tend to grow slowly and metastases may develop years after the primary tumor was removed. A notable example of this is the case reported by Albrecht (1). His patient developed a solitary metastasis to the scapula four years after nephrectomy. This metastasis was removed and the patient was alive nine years after the second operation and thirteen years after the nephrectomy. Barney and Churchill (2) reported a case in which the presenting symptom was referable to the lung, the seat of a solitary metastasis. In the absence of other demonstrable foci, the kidney was removed and fifteen months later the pulmonary lesion, which failed to respond to deep x-ray therapy, was removed by subtotal lobectomy. The patient was alive and in good health five years later.

Of the initial symptoms referable to the urinary tract, hematuria is the most striking one. Judd and Hand (10) found it in 43 per cent of their 367 cases. The same writers found pain in 37 per cent and tumor in 14 per cent. Hyman's (7) series showed hematuria in 41 per cent, pain in 27 per cent, and tumor in 75 per cent. Braasch (3) pointed out that the three are present together late in the disease, long after the diagnosis should have been made.

A relatively early diagnosis which offers the best hope for cure is only possible by complete urological study in the course of routine physical examinations, especially in all cases with an obscure ailment.

In the final analysis, the pyelogram is the only basis on which the diagnosis can be made with reasonable certainty. The pyelographic changes characteristic of renal tumor according to Braasch are : 1) the elongation of one or more calices or of the pelvis; 2) the encroachment on the pelvic lumen, causing a flattening of the general pelvic outline, narrowing of the individual calices, obliteration of the true pelvis, obliteration of one or more calices or complete occlusion at or near the uretero-pelvic junction; 3) secondary pyelectasis; 4) abnormal position of the renal pelvis; 5) deformity at the ureteropelvic juncture and upper portion of the ureter.

Nephrectomy early and as radical as possible offers the best hope for a cure. A solitary metastasis is no contra-indication to operation. If accessible, this should likewise be removed. Bumpus (4) reported a case of spontaneous disappearance of pulmonary metastases following nephrectomy. Beer and others have made similar observations.

The general survival rates reported by Priestley (11) in cases of adenocarcinoma, for three or more, five or more, and ten or more years after operation, were 47.7 per cent, 38.4 per cent, and 27.3 per cent respectively. The lower the grade of malignancy and the lower the weight of the tumor removed, the higher the survival rate. He ascertained these figures from a study of 482 patients who were operated upon in the years 1910 to 1934.

Renal vein involvement makes the prognosis less favorable but not neces-

sarily hopeless. In Hyman's series (9), the survival rate for five or more years after nephrectomy with vein involvement is 16.5 per cent compared to 33.0 per cent when the vein was not involved. One of his patients is alive 19 years after nephrectomy. Albrecht reported two cases living and well, one, four and a half, and the other twelve years after nephrectomy.

X-ray therapy has little or no value in hypernephroma. Postoperative irradiation did not appear to influence the course of the disease or survival rate in cases observed by Walters and Braasch (13); if anything, they state that sometimes irradiation seemed to hasten the end. Hyman draws the same conclusion from the series of cases observed by him.

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THE PROBLEM OF CANCER OF THE ESOPHAGUS

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It is a privilege and a pleasure to contribute to this Festschrift for Dr. Howard Lilienthal. During his long and fruitful career, he has exerted a profound influence on American surgery and this has been particularly noteworthy in his contributions to thoracic surgery. His many diversified interests have always been marked by an unquenchable enthusiasm, a conservative curiosity and a native originality based on sound reasoning. A perusal of his long list of contributions to surgical literature causes one to wonder how he could carry this extra load in addition to a very busy hospital service and private practice.

In 1921, when Dr. Lilienthal made his contribution to the surgery of cancer of the esophagus, definitive surgical treatment of this disease was in its early infancy. While many continental surgeons had thought and talked about it for many years and had devised numerous ingenious procedures, it was not until 1913 that the first successful radical resection was accomplished by Torek. This unique accomplishment by Torek stands out as a milestone in the progress of surgery. The patient, a woman of 69, survived for thirteen years in good health and died of an intercurrent infection. The success of this operation was remarkable because it was carried out at a time when anesthesia in thoracic operations was a major problem and when the physiological aspects of open thoracic operations were little understood.

Torek's success encouraged other surgeons to attempt the surgical treatment of this almost hopeless disease. There appeared in the succeeding years reports by Gluck, Trotter, Gluck and Soerensen, Logan Turner, Küttner, Sauerbruck, Zaaijer, Eggers, etc. That the great majority of these attempts resulted fatally is not to be wondered at, especially when it is remembered that, in those years, the problems of anesthesia and infection, and the paucity of knowledge concerning the physiology of the cardio-vascular and respiratory systems in relation to thoracic surgery presented many handicaps to progress. It was because of this excessively high operative mortality that Lilienthal devised his extrapleural operation. By dividing the operation into stages and confining the operative procedures to the extrapleural space, he minimized and even eliminated pleural infection and obviated the shock of an open pneumothorax. At the same time, he was able to construct a tube to bridge the defect in the

esophagus with the aid of a pedicled flap from the skin of the back. This was preformed, following removal of the cancer-bearing focus. The soundness of his reasoning is demonstrated by the survival of the patient for one year with subsequent death after a local recurrence.

Since then, there has been marked progress in surgical technique, as well as in the field of anesthesia, and there has evolved a clearer understanding of the physiological alterations in the respiratory and circulatory systems incident to thoracic operations. As a result of this progress during the past fifteen to twenty years, surgeons now enter the pleural cavity with the same sureness of success as when opening the abdominal cavity. However, it is during the last five or six years that the radical surgical treatment of cancer of the esophagus has received the serious consideration that it deserves. I am sure I shall not be considered too optimistic if I say that the next few years will see the acceptance of the surgical treatment of this disease by all surgeons, as the only sound method of treatment.

It should be remembered that cancer of the esophagus is usually a slowly growing neoplasm and that it remains a local disease for some time before metastasizing to the regional lymph nodes. But, while it may not spread peripherally until late, it may become locally inoperable in the early stages because of fixation to the nearby vital structures, such as the aorta or bronchus. The importance of diagnosis early in the disease needs little discussion. More rapid progress in the surgical treatment will be made when increasing numbers of early cases are referred to the surgeon. Earlier diagnosis becomes possible when the symptom of persistent dysphagia is investigated by means of fluoroscopic and x-ray examination of the esophagus, esophagoscopy and biopsy.

Until recently, the diagnosis of carcinoma of the esophagus was frequently made late in the disease, too late for surgical treatment. The accepted method of treatment was by radiation methods (x-ray and radium), supplemented usually by gastrostomy. An enormous experience with these modalities has accumulated throughout the world and a critical review of the results is possible. A survey of the literature on the subject indicates that the results of radiation therapy have been universally disappointing. Of the vast number of patients treated by these methods, approximately twenty are said to be cured and many of these are open to question either because the follow-up period was too short or because the histologic evidence of carcinoma was incomplete or inconclusive. I believe it is fair to say that, if surgeons had the opportunity of operating upon the large number of early cases now being referred to the radiologists, the surgeons' results would be incomparably better than any the radiologists have been able to report.

The best results of surgical treatment, both immediate and late, follow the combination of early diagnosis, careful pre-operative preparation, a sound operation based on our present day conception of radical cancer

surgery, expertly administered anesthesia, meticulous postoperative care, and the immediate treatment of complications as they arise. This calls for maximum effort on the part of a well-trained personnel from the beginning to the termination of treatment.

It has seemed convenient, in discussing the operative treatment of cancer of the esophagus, to divide the organ into thirds. The upper third, extending from the hypopharynx to the arch of the aorta, presents an altogether different surgical problem than is encountered in the middle and lower thirds. The middle third extends from the aortic arch to a point about 33 to 36 cm. from the upper incisor teeth. The length of this portion varies somewhat with the height of the patient. The lower third extends to the cardia of the stomach. It is apparent that it is important for the esophagoscopist to locate accurately the position of the neoplasm. This information helps the surgeon to decide which operative procedure he will choose.

Until recently, it was thought necessary to perform gastrostomy preliminary to the resection of middle third growths. Recently, however, I have changed the plan of procedure for patients in fairly good condition. Practically every type of gastrostomy operation is followed by annoying leakage of gastric contents through the opening. To obviate this, I now preserve the lower two inches of the organ (following resection of the tumor-bearing portion), leaving it attached to the stomach, and bring it out through a small abdominal incision where the divided end is sewn to the skin to form an esophagostomy. In this way, the sphincteric mechanism of the cardia is preserved and leakage does not occur. Thus, the operation is completed in one stage. The operating time varies between two hours and fifteen minutes and three hours. This recent change in technique will greatly simplify the subsequent construction of a skin-lined tube on the anterior chest wall to replace the resected esophagus, obviating the use of a rubber tube.

The ideal operation is one which includes removal of the tumor-bearing portion of the organ together with a wide margin of normal tissue, and reestablishment of esophago-gastric continuity by some type of anastomosis. When the cancer is located in the middle third of the organ, this cannot be done and the makeshift procedure above outlined must be carried out. However, when the growth involves the lower third of the esophagus, this ideal can be attained. Through a left transpleural approach, it is possible to resect the distal third of the organ, incise the left leaf of the diaphragm, mobilize the stomach and perform an end to side anastomosis between the cut end of the esophagus and the anterior wall of the stomach. At the completion of the operation, the proximal half of the stomach occupies an intrapleural position. In a fairly large group of successful resections of this type, there has been remarkably little disturbance of esophageal or gastric function.

Statistics, especially in small series of cases, ordinarily have very little value. However, in a newly-developing field of endeavor, they are of considerable importance in indicating whether encouraging progress is being made. In addition, by analysis of the operative mortality one can deduce the risk of subjecting a patient to so radical a procedure. It is particularly important to stress that, especially in a small series, survival statistics may be materially influenced by the recovery or death of one patient. During the past four and one-half years, I have operated upon twenty patients with squamous cell carcinoma of the esophagus. Fourteen patients were found to present operable lesions, an operability rate of 70 per cent. In the group of fourteen patients subjected to radical resection, there were five deaths, an operative mortality of 35.7 per cent. Of the nine survivors, five are alive and well today, one almost four years, one eighteen months, one thirteen months, one seven months and one six weeks. The remaining four patients died of local recurrence or other cause twenty-two months, one year, one year and three and a half months respectively after operation.

In contrast to this group of patients, I would like to mention briefly our experience with adenocarcinoma of the cardiac end of the stomach with esophageal obstruction. During the same period of time, I have operated upon fifteen such patients. Only five presented operable lesions, an operability rate of 33.3 per cent in contrast to the 70 per cent in the preceding group. Of the five patients subjected to resection with intrathoracic esophago-gastric anastomosis, two succumbed, one of cerebral embolus on the third day and one to inanition and general debility on the third day (autopsy negative). The surviving patients are alive and well, fourteen months, four months and three months respectively after operation.

The statistics given above and the experience reported by other observers indicate that rapid progress is being made in the treatment of a disease heretofore considered to be hopeless. We have now reached a stage in the surgical therapy of cancer of the esophagus where we can assure the patient of a reasonable chance of survival. Dr. Lilienthal's contribution to the subject indicated the feasibility of safe surgical attack and gave encouragement to surgeons in later years to extend the field of applicability of the principles so clearly enunciated by him.

THE THERAPEUTIC VALUE OF IMPLANTED ESTROGENS

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Following the demonstration by Deansley and Parkes (1, 2) that prolonged estrogenic effects resulted from the subcutaneous implantation of estrogenic substances, it was decided to determine whether it would be possible to prolong the physiological effects and clinical relief in humans, of a given dose of estrogenic hormone by implanting the estrogen subcutaneously. It appears from the results of various investigations that the high dosage of estrogens required to relieve symptoms caused by ovarian failure and to maintain the endometrial and vaginal mucosa in a normal physiological state is, in a great part, attributable to the rapid absorption and excretion of the hormone. To achieve a satisfactory therapeutic effect at present it is necessary to administer intramuscular injections of a solution of the hormone in oil at frequent intervals, for periods of many weeks. The effect of oral therapy is still not entirely satisfactory. Aside from the inconvenience caused the patient by the necessity for frequent injections, there is the additional factor of expense which places this form of therapy beyond the means of the majority of patients. In the interest of economy and the patient's comfort, it would appear to be highly advantageous to have an estrogenic preparation which would be absorbed slowly so that the patient may derive a fuller measure of benefit from a given amount of the hormone, thus obviating the necessity for frequent injections. An attempt was made by my associates and myself (3, 4, 5, 6, 7) to achieve this objective by the implantation of crystalline estradiol and estradiol benzoate. The implants were of two types, the ordinary crystals varying from 4 to 58.6 mg. in weight, and compressed crystals in the form of pellets varying from 15 to 50 mg. in weight.

Technique. The hormones were placed in small glass tubes measuring 3 mm. in diameter and 1.5 cm. in length and sterilized by autoclaving. The implantation was performed in the gluteal region. The skin was prepared with tincture of iodine and alcohol. An area of skin measuring approximately 1.5 inches in diameter was infiltrated with 2 per cent novocaine. An incision measuring 1 inch in length was made and the capillary oozing controlled with a dry packing. The estradiol benzoate crystals were then implanted into the wound and the skin edges approximated with two silk sutures. The sutures were removed five days later. Pellets were implanted in the same manner, one or two pellets being placed in the wound and the wound sutured. The absorption rate of implanted

pellets of a-estradiol and a-estradiol benzoate was studied (6) and compared with the absorption rate of a similar amount of uncompressed crystalline hormone. The comparative duration of the physiological and therapeutic effects of pellets and of crystals of the same estrogenic compound were also noted. During a period of observation of approximately one year it was found that more prolonged physiological and therapeutic effects resulted from the implanted crystals than from the pellets of similar weight and chemical composition. It was deemed important to determine the absorption rate of the hormone by removing and re-weighing the implanted pellets at varying intervals after implantation. At the same time, the duration of biologic effects of the implanted hormone, as manifested by morphologic changes in the endometrium and vagina mucosa, were studied by means of repeated vaginal smears and vaginal and endometrial biopsies.

From the 46 cases implanted with pellets, 14 patients (9 natural menopause, 4 surgical castrates and 1 roentgen-ray castrate) were selected for excision of the pellets. The duration of the menopause in this group varied from 2 months to 7 years. All of the patients had either clinical or morphologic evidence of estrogen deficiency, or both, prior to the implantation.

Round, flat pellets of a-estradiol and a-estradiol benzoate, sterilized by autoclaving (265°F. at 15 pounds pressure for 30 minutes), varing in weight from 15 to 25 mg. each, were implanted, subcutaneously, in the center aspect of the thigh. Nine patients were implanted with a single pellet, four with 2 pellets, and one with 3 pellets. In 8 cases, the pellets were composed of a-estradiol and in 6, of a-estradiol benzoate. The implantation sites were excised at varying intervals after the implantation and the pellets were weighed after drying in a desiccator.

Absorption Rates of A-Estradiol Pellets. The a-estradiol pellets were excised at periods of time varying from 130 to 245 days following the implantation. Each pellet was found to be closely enveloped by a fibrous capsule (Fig. 1). Histologic study of the surrounding tissue revealed a typical non-specific foreign body reaction. (The histologic details of the tissue reaction to the pellets have been described elsewhere (7)).

The rate of absorption, expressed in terms of average percentage weight loss per 30 days, varied from 1.9 per cent to 8 per cent, with an average for the series of 4.85 per cent. This represents, in terms of rat units, daily absorption rates varying from 191 to 1460 R.U., with an average for the series of 473 R.U. per day. Deanesley and Parkes (1, 2), in their study of a-estradiol pellets implanted in rats, reported 6 to 9 per cent average absorption per month.

Absorption Rates of A-Estradiol Benzoate Pellets. The a-estradiol benzoate pellets were excised at intervals varying from 87 to 207 days after the implantation. In this series, also, a fibrous capsule was found surrounding each pellet. The rate periods varying from 45 to 75 days; one (case 12) was symptom-free at the time of excision, which was 88 days

after the implantation. It is apparent from this study that pellets of *a-estradiol* have a more prolonged therapeutic and biologic effect then pellets of *a-estradiol benzoate.*

It is important to note that despite the presence of sizeable pellets (weighing 11 to 46.4 mg.) in the subcutaneous tissue, the majority of the patients, at the time of excision, exhibited clinical as well as morphologic evidence of estrogen deficiency. The fact has already been mentioned that the pellets were found to be completely enveloped by a tight, fibrous capsule (Fig. 1). Apparently the capsule acts as a barrier, progressively retarding absorption of the hormone and reducing it finally to a level at

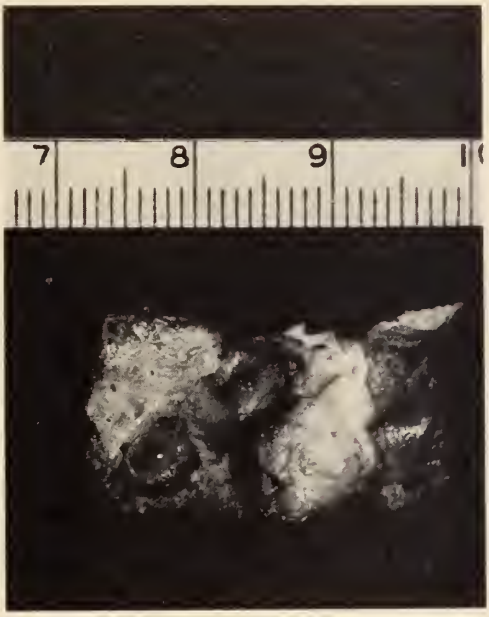

FIG. 1. Thick fibrous capsule surrounding the implanted pellets

which no demonstrable estrogen effect is exerted, either clinically or morphologically.

The question may be raised whether the hormone may not be inactivated by its prolonged contact with the subcutaneous tissues. Such a qualitative change in the pellets has been considered and ruled out by demonstrating that the excised pellets, when re-implanted in rats, produced characteristic estrogenic effects.

It is evident from this study that, in spite of the striking initial morphologic and therapeutic effects produced by the implanted estrogen pellets, there is a serious objection to this method of administering estrogens clinically, since the therapeutic effect is relatively short-lived and the patients, thereafter, retain sizeable pellets without deriving any therapeutic benefit from them.

The duration of biologic and therapeutic effects was definitely longer in the a-estradiol series. It was concluded, on the basis of these studies, that the fibrous capsule which forms about the pellets progressively decreases the rate of absorption of the hormone, so little being absorbed finally that no demonstrable morphologic or therapeutic effect is produced. Furthermore, because of the fact that absorption of the hormone in effective amounts ceases when only a relatively small amount of the pellet has been absorbed, it is concluded that the implantation of pellets (weighing 15 to 25 mg.) of a-estradiol and a-estradiol benzoate is not a satisfactory method of administering estrogens clinically.

It was realized also that the study of the tissue reaction to the prolonged contact with varying amounts of estrogenic hormone must be undertaken. The local tissue response to the implanted estrogen crystals and pellets, therefore, was investigated (7). Fourteen patients (of whom 8 had had a spontaneous menopause, 4 were surgical and 2, roentgen-ray castrates), were selected for excision of the implanted hormone and surrounding tissues. Ten patients had been implanted with pellets (5 a-estradiol and 5 a-estradiol benzoate). All of these cases, before the implantation, had typical menopausal symptoms and morphologic evidence of estrogen deficiency as indicated by negative vaginal smears and biopsy specimens showing atrophic vaginal mucosa and endometrium. The amount of hormone implanted varied from 15 to 50 mg. The individual pellets weighed 15 to 25 mg. Four patients were implanted with crystals of a-estradiol and a-estradiol benzoate, varying in weight from 10 to 23 mg. The implantation sites were excised under local anesthesia (1 per cent novocaine) at periods varying from 23 to 238 days after the implantation, the excised material including the skin and surrounding tissues. The pellets were removed and the excised tissue was fixed in 10 per cent formalin. Serial sections were made and stained with hematoxylin and eosin. In none of the cases implanted with crystals were we able to find any gross evidence of the crystals at the time of excision.

It was noted that a fairly uniform tissue reaction occurred in each case. The pellets were completely surrounded by a fibrous capsule (Fig. 1) which varied in thickness depending upon the duration of implantation. The pellets retained their original shape and consistency and, although intimately adherent to the capsule, could be easily shelled out. The subcutaneous tissues showed a typical foreign body reaction. Each of the capsules showed essentially the same histologic picture. The protocol of a typical case is presented here.

This patient (D. N.) had implanted in the subcutaneous tissue of her right thigh, two pellets of a-estradiol benzoate (total weight 50 mg.) and the implant-site was removed 88 days later. The tissue showed a thick, sharply demarcated capsule. The significance of the thickness of the capsules has already been mentioned.

The capsule (Fig. 2) consists of three, more or less, distinct layers surrounding a central cavity. The inner layer adjacent to the cavity consists of two zones: (a) an inner zone which is composed of one to three layers of cells which are elongated, narrow and eosinophilic and contains irregular nuclei which have no uniform cell position, and (b) an hyalinized connective tissue zone containing scattered lymphocytes, polymorphonuclears and some large, pale-staining cells with oval nuclei. The nuclei of these large cells have a well defined chromatin content, the cells resembling phagocytes. The middle layer is a slightly wider area, which is supported by a hyalinized connective substratum and is infiltrated by many closely packed, small, round cells (lymphocytes and plasma cells), fibroblasts, occasional leucocytes, and a scattering of giant cells. The outer layer consists of a relatively narrow band of hyalinized fibrous tissue which contains some

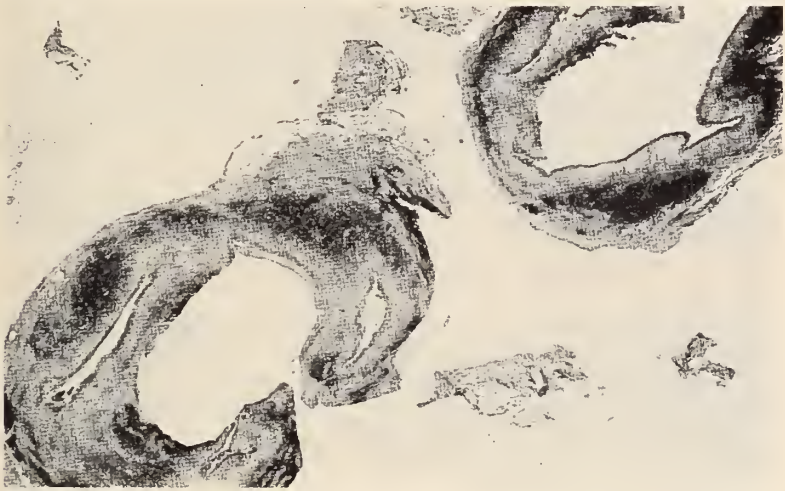

FIG. 2. Capsule about pellets, showing layers (low power)

dilated lymphatic vessels. The surrounding fat tissue shows slight edema and contains a few lymphocytes and giant cells. The skin overlying the implanted pellets is normal.

On excision of the implantation sites of the crystals, no macroscopic capsule could be seen. On cut section one could, however, discern multiple, pin-point, grayish areas distributed throughout the subcutaneous fat tissue. Figure 3 is a low power photograph of a gross section of an implantation site removed from patient L. S. who had been implanted 236 days previously with 10 mg. of a-estradiol crystals. One can clearly see in this section at least 14 minute, discrete conglomerations of cells, which have the appearance of small tubercles. With higher magnification (Fig. 4), the resemblance of these accumulations of cells to foreign body tubercles becomes even closer.

These tubercles consist of a central core of tissue containing several cavities of variable size, which are delimited by fine connective tissue septa. The latter contains many irregular nuclei which vary considerably in size and shape. Some of the nuclei are giant-sized and no separate cell margins can be identified. This central core is surrounded by a zone

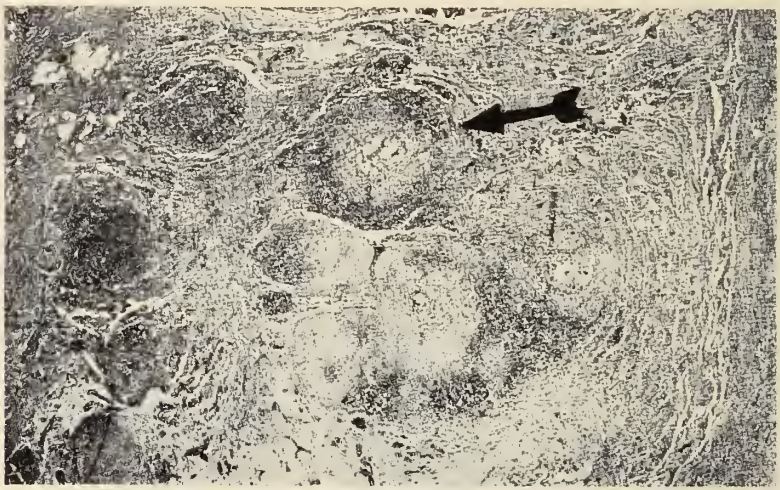

FIG. 3. Implantation site of estrogen crystals (low power)

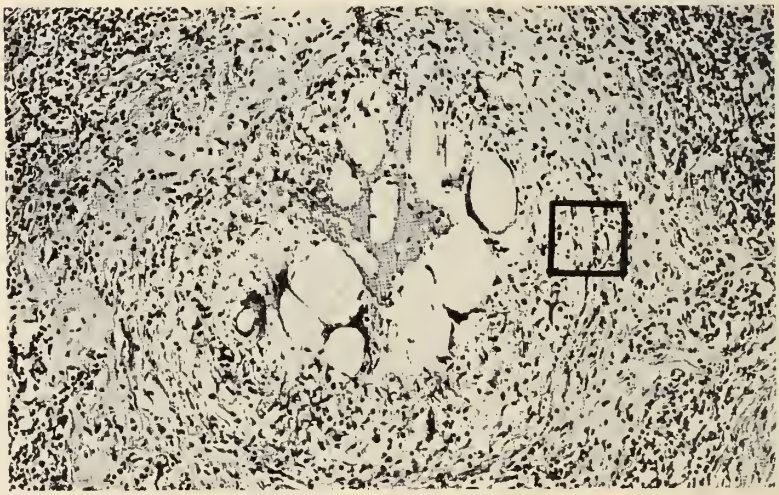

FIG. 4. Area marked by arrow in Fig. 3 (higher magnification)

of hyalinized tissue which contains numerous irregularly shaped cells with large vacuoles and a scattering of foreign body giant cells.

Surrounding the above described central structure are three layers of cells which resemble, in miniature, the three layers of cells which make up the gross capsule previously described.

The local tissue response to implanted crystals and pellets is a typical non-specific foreign body reaction. It is important to note that the epidermis overlying the implants showed no evidence of cellular atypism and, similarly, in no instance did the subcutaneous tissues in contact with, and adjacent to, the implanted hormone show any abnormal cellular proliferation.

A significant observation which emerges from this study is the probable effect that the thick avascular capsule has on the absorption rate of the estrogenic substance employed. It was noted that the crystals had a strikingly more prolonged therapeutic and physiologic effect than the pellets composed of the same estrogenic substance and of comparable weight. It would appear, therefore, that the capsule might have a marked retarding effect on the rate of absorption of the hormone. Apparently, with the passage of time, the absorption rate is progressively diminished by the growing thickness of the capsule around the pellet. After a period of approximately three months, absorption is either completely stopped or so reduced as to have no demonstrable physiologic or therapeutic effect. It seems, therefore, that for purposes of implantation, pellets of a-estradiol and a-estradiol benzoate are not as efficient as crystals of the same chemical constitution.

SUMMARY

The clinical investigation of the effectiveness of implanted crystals and pellets can be summarized from a study of 117 cases. Thirty-three cases were implanted with *estradiol crystals*, the weights of which varied from 4 to 50.6 mg. All of these cases were post menopausal, either of natural origin or as a result of operative or radiotherapeutic castration. All showed biologic indications of estrogen deficiency before treatment. But during the period of observation, which varied from two to fifteen months, the vaginal smear became positive and the vaginal and endometrial biopsies showed definite evidence of estrogenic stimulation. The gonadotropic hormone inhibition lasted up to 160 days with doses of 25 to 50.6 mg. Clinically there was complete relief in 29 cases, incomplete relief in 3 cases and no relief in one case. A group of menopausal cases, similar to the above, numbering 39 were implanted with *estradiol benzoate crystals*. Ten of the cases were implanted with approximately 25 mg. each at the time of operative castration as a prophylactic measure against the development of menopausal symptoms. All ten have remained symptom free for the period of observation namely from two to eight months. The other 29 cases in this group received from 6 to 29 mg. by implantation. The biologic response changed from that of an estrogen defficiency to that of an estrogen stimulation. The gonadotropic inhibition lasted up to 95 days with doses varying from 25.3 to 27.2 mg. In 25 of the 29 cases there was complete relief, in three partial relief, and in one no relief.

The results, both morphological and clinical, were not as good in the

cases with implanted pellets. Twenty-three cases were implanted with *estradiol* pellets the weight of which varied from 15 to 50 mg. In only eighteen was the relief complete for the period of observation. In four there was incomplete relief and in one no relief. Of the twenty-two cases implanted with *estradiol benzoate* pellets weighing from 15 to 50 mg., the morphological and biological response was of comparatively short duration. The gonadotropic hormone inhibition lasted only thirteen days. Of the twenty-two cases, fourteen had complete relief, six incomplete relief and two, no relief.

In contrast with the long period of gonadotropic hormone inhibition resulting from the implanted estradiol or estradiol benzoate crystals, 50 mg. of estradiol benzoate *in oil* injected intramuscularly inhibited the gonadotropic hormone for only ten days.

CONCLUSIONS

Fom the results of these observations it is evident that the implantation of estrogenic hormone is superior to the injection of the same material in oil, from a clinical, biological and morphological viewpoint. It is also evident the therapeutic effects of the implantation of crystals are far superior to that of pellets. It is suggested that this is due to the more even and longer absorption rate from the crystalline implant because of the failure of the surrounding tissue to develop a thick fibrous capsule about the implant. Finally it is important to realize that in spite of the contact of the tissue with large doses of estrogenic hormone for a long period of time it fails to show any growth stimulation or atypical cellular proliferation suggestive of hypertrophy or lawlessness.

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PRIMARY NEUROECTODERMAL BRAIN TUMORS; THEIR TRANSITION FROM BENIGN TO MALIGNANT FORMS[1]

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INTRODUCTION

The opinion is often expressed that a benign tumor may, at one time or another in its life cycle, acquire the character of a malignant growth. This transformation is more often assumed by the clinician than verified by the pathologist. However, it is occasionally encountered in brain tumor; and it probably occurs more frequently than is commonly observed. The failure to establish with certainty such a change was due in the past to clinical difficulties and particularly so to the unavailability of necessary pathological material. Clinically there is much variation in the length of time of onset and the course, leading to a stormy and inevitably fatal termination, is frequently atypical. Symptoms of great variety result from anatomical and pathological factors peculiar to the brain. Moreover, to the general symptoms of increased intracranial pressure caused by an expanding lesion, other symptoms of great complexity are added from the implication of specialized neural regulatory mechanisms mediating the far-flung influence over the visceral and somatic organs and tissues. On the pathological side, the failure was due in great measure to the lack of opportunity during the clinical course, to distinguish accurately, by means of histological studies, the cellular alterations indicating the probable transition from a benign to a malignant tumor. However, with the recent advent of more militant intracranial surgery, a more thorough study of the various phases in the evolution of brain tumors was made possible. Recurrences in surgically treated gliogenous growths led to surgical revisions. In this way, material revealing early stages of formation as well as subsequent histologic alterations in the later course of development of the tumor became available.

This study is based on the investigation of a rather small group of cases, hence it does not carry the emphatic reply to the question as to how a benign growth acquires malignant features. But it contributes important information on a related question and its share in support of the accumulating evidence that brain tumors, as do tumors elsewhere, consist of cells, which morphologically recapitulate one or another histogenetic phase of the primordial cells which serve as the germinal center of the tumor.

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Moreover, it reveals that variable numbers of these primordial cells, conspicuous or hidden amidst fully differentiated cell types or among transitional cell forms, are almost always present, and may be discovered if searched for diligently and systematically.

The pathologist accepts the predominance of one or another cell type in the scale of differentiation, as a rough indicator of the character of the tumor, whether benign or malignant. The occurrence of tumors, in which the transitional cell type dominates the field, thereby often causing great difficulty in placing the tumor in one of the two categories, i.e., benign or malignant, serves to show that too sharp a line of demarcation cannot be drawn between them. This is a rather common experience in the case of gliogenous tumors.

The above observations are, of course, in accord with the Cohnheim-Ribbert embryonal rest theory. They permit the assumption that in each tumor there are one or more aggregations of primordial cells, which constitute the growth centers of the tumor. Under conditions favoring the proliferation of these immature cells, this process may be rapid and carried out on a large scale, with the cell division speeding far ahead of the normal process of cell differentiation. In this manner, there are produced numerous cells with wide variations in their state of maturity. Many of them, for lack of favorable physiological conditions, disintegrate and, in this fashion give rise to more or less extensive areas of necrobiosis. Very likely, such are some of the conditions which are productive of growths, identified clinically and anatomically as malignant. When, however, the primordial cells multiply slowly and over extended periods of time, they may complete their full differentiation. Thus, tumors are evolved consisting of mature cells with features common to the so-called benign growths. With this scheme of tumor formation in mind, the relation of the benign to the malignant growths and the transition of the former into the latter may be envisioned. For, if it is true, that in each tumor, no matter what the predominant character of its cellular constituents may be, there are hidden aggregations of cells, endowed with the inherent potency of proliferation and differentiation, the transition of morphologically mature type of newgrowth into the malignant form is always within the limits of probability during its life cycle. It is conceivable, moreover, that were the life of the host indefinitely prolonged every benign tumor might ultimately evolve a malignant growth, provided the germinal nucleus of the growth were not entirely exhausted.

The above hypothesis for the metamorphosis of benign neoplasm into malignant seems to have its advantages over the theory of anaplasia proposed by Hanzeman (1) and supported by Ewing (2), which is used in the explanation of the phenomenon of such transition. According to the latter it would be necessary to accept the view that a new cell unit, capable of reverting to the primordial type is evolved and that this cell is instru-

mental in the evolution of malignant growths. However, both theories can be brought into accord, if it is agreed to interpret anaplasia as the loss of normal differentiation, function and organization on the part of the tumor cells, as defined by Ewing.

THE TERM SPONGIOBLASTOMA MULTIFORME

This paper, as will be noted, is especially concerned with a group of gliogenous tumors, which in the early stages of formation presented clinical and morphological features suggesting a relatively benign character, such as are displayed by gliomas and in some instances, by the so-called transitional gliomas. In the course of their growth, these tumors have been converted

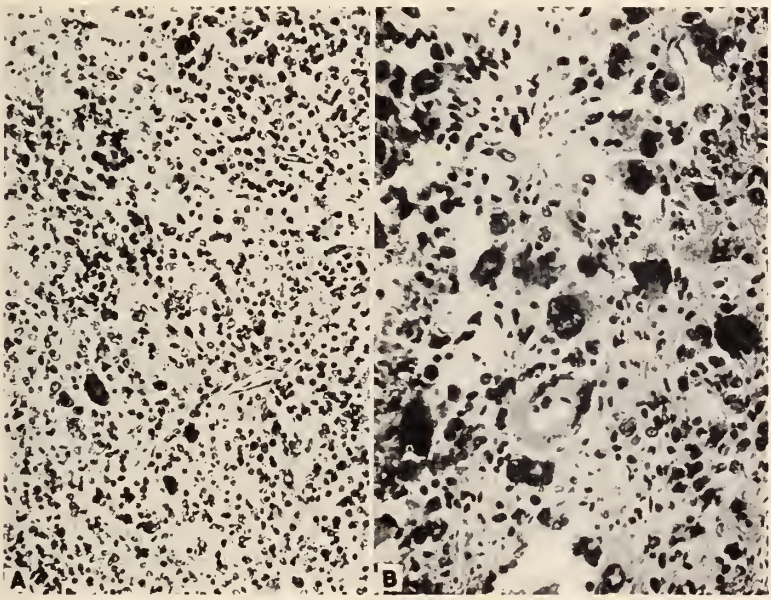


FIG. 1. A. Microscopic appearance of spongioblastoma multiforme.
B. Giant cells typical of spongioblastoma multiforme, under higher magnification.

into the more malignant forms finally evolving the anatomical character of primary malignant brain tumors, such as are now termed Spongioblastoma Multiforme and spongio-neuroblastoma. The term *spongioblastoma* was first adopted in 1918 (3) for gliogenous growths consisting predominantly of undifferentiated glial cells, the so-called spongioblasts, and which were previously described under such names as, *giant cell glioma* because of the presence in such a tumor of a large number of giant cells; *Adenoglioma*, for the alveolar cellular arrangement frequent in the microscopic field; *Neurocpithelioma gliomatosa*, a term, not at all unjustified, because of the undifferentiated character of the glial elements; *glioma ganglioneare*, to denote the presence of giant cells bearing some resemblance to ganglion cells; and *glioma telangiectaticum*, to emphasize the wealth of

blood vessels. In the spongioblastoma multiforme the spongioblasts, arrayed alongside of numerous other atypical cell-forms, including many giant-like cells, are arranged in a characteristic manner (fig. 1).

Additional studies on spongioblastomas were made in 1925 (4), and their anatomical character and their clinical features were summarized under the title of "Spongioblastoma Multiforme." The qualifying term multiforme was added at the suggestion of Dr. Harvey Cushing, to stress the multiformity of the cellular elements in the type of tumor, and to indicate that it differed from a tumor which in collaboration with Bailey (5), Cushing first decided to call Spongioblastoma and then renamed Medulloblastoma.

TRANSITIONAL GLIOMA

As already indicated, the histologic identification of the several types of glial tumors often offers great difficulty because of the wide range of differentiation of their cellular components. The practice to assay and name a given tumor in accordance with a dominant typical cell form does not always yield satisfactory results, for the cells which constitute the bulk of the neoplasm may be in a state of transition between a primitive cell form and those of a more completely differentiated cell type. Under such circumstances, it was found advisable to designate such tumors as *transitional glioma* (6).

In general, the histologic features of such a gliogenous brain tumor may be summarized as follows: The tumor has no sharp line of demarcation, the neoplastic tissue merging with variable directness into an area of reactive gliosis, which was usually fairly well defined. The gliotic zone is composed principally of fibrous astrocytes, which are not infrequently larger than those present in the normal cerebral tissue. The tumor tissue in all cases is extremely vascular, but there are also areas in which the vessels are few or moderate in number. The vessels are marked by the hyperplastic endothelium, which frequently leads to occlusion of the vessel. This type of vessel is not infrequently seen beyond the limits of the tumor, within the peripheral gliotic zone. In a few instances the vessels are of a more primitive sinusoidal nature, and in others they seem to have proliferated in a manner reminiscent of vascular channels in hemangiomata. Scattered throughout the tumor there are hemorrhages of varying extent, ranging from those recognizable grossly to minute miliary aggregations of erythrocytes. Areas of necrosis are frequent and generally quite extensive. About such areas there are usually large collections of component granular cells. The neoplastic cells are, in the main, of a fairly consistent uniformity, in type and arrangement (fig. 2). The cells, predominantly unipolar, frequently bipolar and occasionally multipolar, are poorly differentiated and not remote from a form usually grouped with the spongioblasts. A feature illustrative of the more mature form of the constituent cells is the production of a fibrillar reticulum.

With silver and gold impregnation technics there were identified in each case cells of every degree of differentiation, from those resembling apolar spongioblasts to those suggesting mature astrocytes. The blastomatous nature of the simpler cells was often evidenced mainly by their arrangement and profusion rather than by their individual form. The undifferentiated forms resembling bipolar or unipolar spongioblasts and those with three or more processes apparently comprised almost totally those areas in which some cellular pattern was evident; elsewhere they were still more numerous than the more mature types among which they were scattered. A single area in one tumor was composed of giant astrocytic cells in a meshwork of their processes.

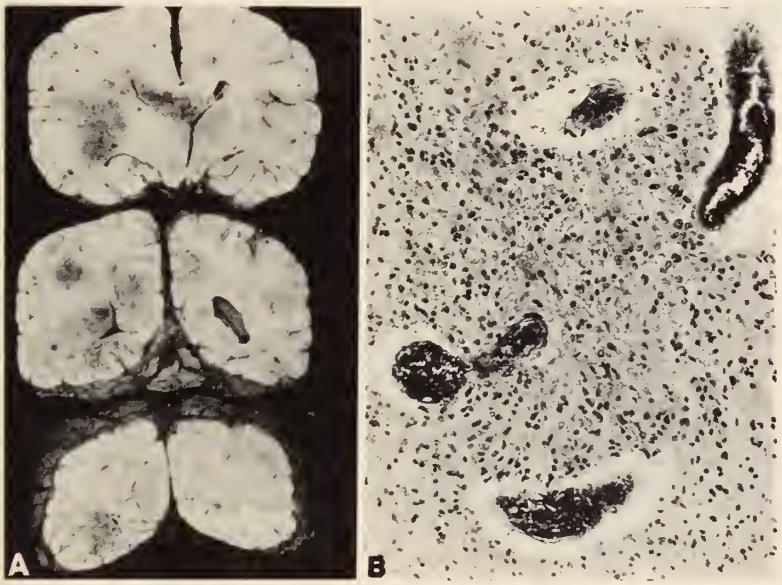


FIG. 2. A. Transitional glioma; gross appearance of the tumor; note its tendency toward multiple centers of growth.
B. Microscopic appearance of transitional glioma (compare with figure 5B).

In general, the transitional glioma occupies a position in the scale of cellular differentiation closer to the spongioblastoma than to the astrocytoma, though some display areas which must, by themselves, be regarded as composed of relatively ripe glial cells.

GLIONEUROMA AND SPONGIONEUROBLASTOMA

Experience with primary neuroectodermal brain tumors grew and it became evident that there is a fairly large group of such tumors which are composed of both neural and glial elements. The existence of such tumors could be readily postulated on purely theoretical grounds when it is realized that the primitive neuroepithelium, a likely source of brain tumor formation, is also the source of both glial and neural elements. Accordingly

such tumors were designated as glioneuroma and spongioneuroblastoma (7) and they are related to one another as gliomas are to spongioblastomas.

THE GLIONEUROMA

Histologically, it displays a remarkable uniformity in cellular contents and arrangement. There are large numbers of fairly well differentiated nerve cells distributed among fairly dense masses of equally well differentiated neuroglial elements (fig. 3). The nerve cells have as their characterizing features the relatively small size of the cell body, the paucity of cell processes for the majority of cells, and the rather restricted amount

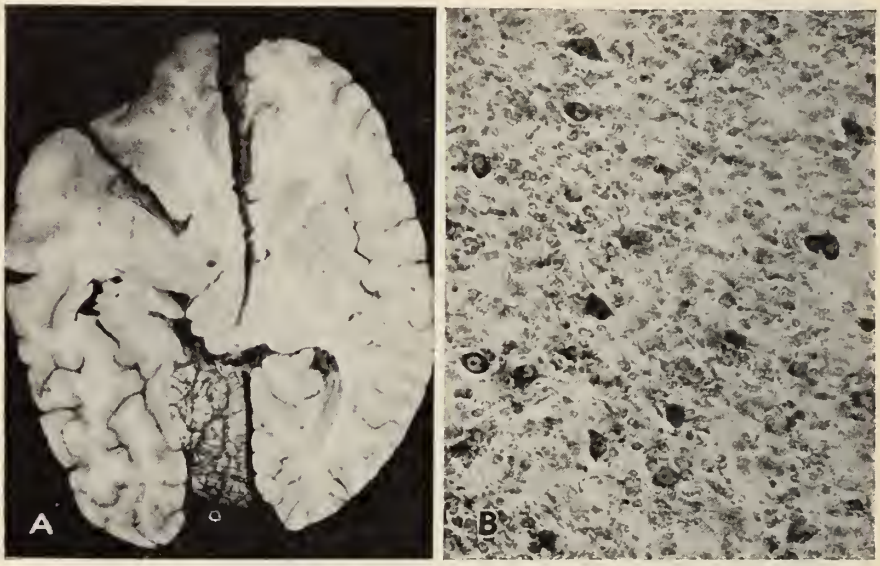


FIG. 3. A. Section of the brain showing enlargement of the left hemisphere, particularly that of the frontal lobe, the seat of a poorly demarcated tumor. This appearance is characteristic of glioneuroma.

B. The microscopic appearance of a glioneuroma showing quite ripe nerve cells surrounded by many faintly stained glial cells.

of Nissl substance. The glial elements also have small cell bodies and short and delicate processes. They bear a strong resemblance to glial elements in the young brain. Undifferentiated elements, such as neuroblasts and spongioblasts, are found in small numbers; equally inconspicuous in the majority of instances are the giant and other anomalous cells

THE SPONGIONEUROBLASTOMA

The spongioneuroblastoma, as already indicated, consists of cell types of a lineage similar to those of the glioneuromas, except that in the spongioneuroblastoma they are of a more primitive character. The glial derivatives here are spongioblasts, encountered in the related tumor form

known as spongioblastoma multiforme, and they, similarly, assume the character of pyriform elements and the multinuclear giant type cells not to the exclusion of more differentiated glial cells. Added to these cell forms, the spongioneuroblastomas contain varying quotas of neuronic

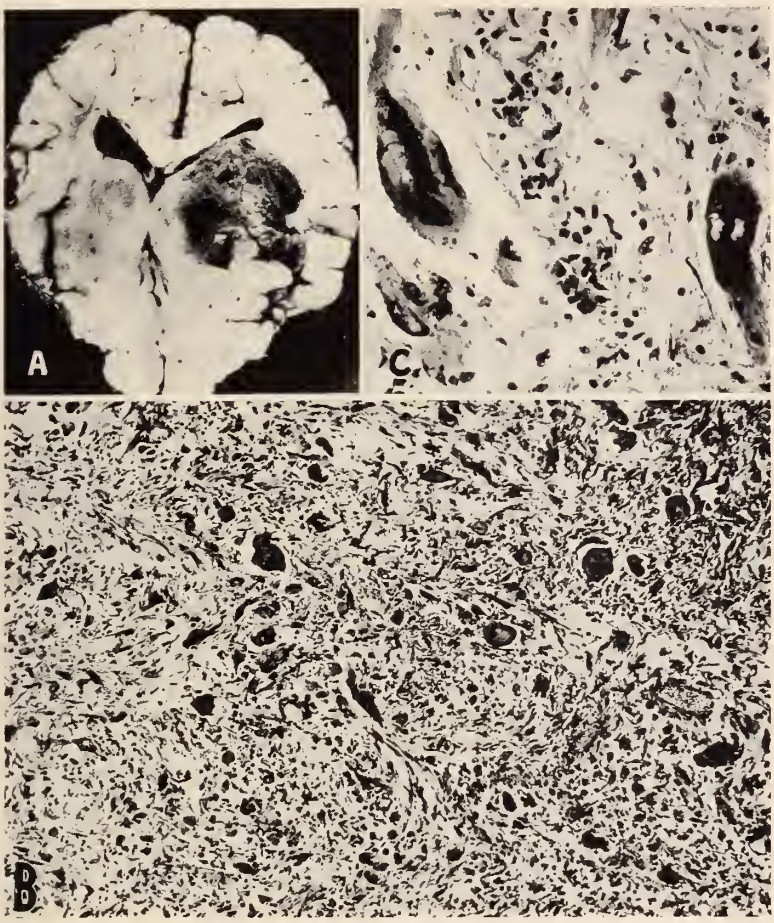


FIG. 4. A. The gross appearance of a spongioneuroblastoma; it bears a strong resemblance to spongioblastoma multiforme.

B. The microscopic appearance of spongioneuroblastoma; note the grouping of the giant cells.

C. Monstrous giant cells in spongioneuroblastoma bearing a strong resemblance to the monster cells in tuberous sclerosis.

elements in the early stages of maturation and also present, in various parts of the brain at various distances from the tumor, disseminated hyperplastic lesions, similar to those found in tuberous sclerosis. The coexistence of spongioneuroblastomas with lesions typifying tuberous sclerosis has been designated as spongioneuroblastoma disseminatum.

THE HISTOGENETIC LINEAGE OF THE TUMORS UNDER DISCUSSION

In previous contributions on this subject schemas were presented to indicate roughly the process of transition or differentiation of gliogenous and neural elements. None of these, nor the accompanying schema give the final word in portraying the several phases in the process of differentiation of the neuroepithelium. But as outlined here it presents a workable plan, and its value is enhanced by its conservative character, a feature, which is essential in a field that is new and open to many errors. The histogenetic process as indicated in this schema, in spite of the gaps incident to any artificial plan, should be understood as an uninterrupted chain in the course of cell differentiation. However, for purposes of classification of tumors, each cell type linking this chain may be regarded as a "seed cell" capable of evolving a tumor type, to which it contributes the dominant cell-form and hence its histologic character. It must also be borne in mind, that, though a given link may be the main source of origin of the tumor, the latter, because of the continuity of the chain, may include many elements derived from the adjacent links and, hence, give rise to a multiformity in its histologic appearance. This is very likely the reason why pure gliogenous tumors, consisting of one type of cell only, are rare and why in every type of glioma a quota of lower or higher grades of cell differentiation will be detected. But, in spite of the fact that transitional phases are seen in every tumor, it is, nevertheless, possible on recognizing the predominance of certain cellular elements, to identify separate forms of gliogenous tumors under the following categories: *Neuro-epithelioma, ependymoma, spongioblastoma multiforme, neurospongioblastoma, glioneuroma* and *glioma.* More elaborate classifications have been proposed but their merits and flaws need not be considered here.

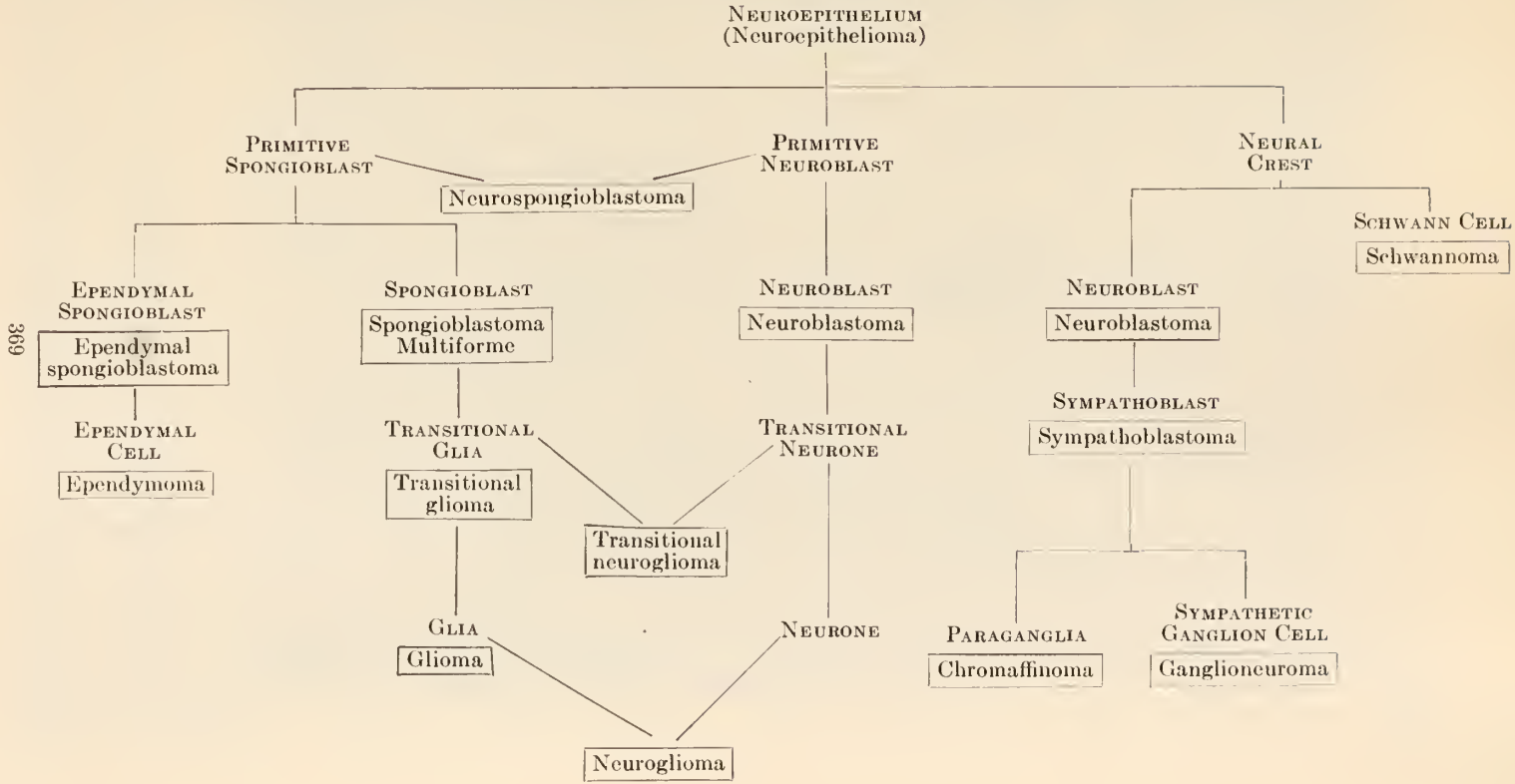
CASE REPORTS AND ANATOMICAL OBSERVATIONS

Case 1. *Gradual development of signs of brain tumor. Craniotomy; tumor revealed; diagnosed glioma; recovery; recurrence; second craniotomy; spongioblastoma multiforme disclosed; improvement; recurrence; death; necropsy.*

History. L. B., aged 30 years, was suddenly seized with a generalized convulsion. During the attack, he lost consciousness for several minutes. Later, in the same year he passed through a similar attack. One year later these attacks reappeared, but now they were preceded by the sensation of electrical shocks in the fingers of the left hand, which traveled up the arm and left side of the chest to the left side of the neck. These attacks recurred about every three months for a period of two years, and then followed an interval of two and a half years, during which he was free of convulsive seizures but would occasionally experience the peculiar "electric" sensations in the left forearm. On two occasions there was a loss of bladder control. Seven weeks prior to admission, he had another convulsive seizure, following which he noted gradual impairment of sensation in the left hand and that objects would fall out of his hand without his being aware of it. He began to drag his left leg and in

TABLE I

A schematic outline of the histo-genetic stages in the development (maturation) of the neural, glial and ependymal elements of the nervous system with an indication of their relationship to the several forms of neoplasms, neuroectodermal in derivation.



in speaking, he would often find difficulty in finding the right word. The week preceding his admission to the hospital was marked by severe headache.

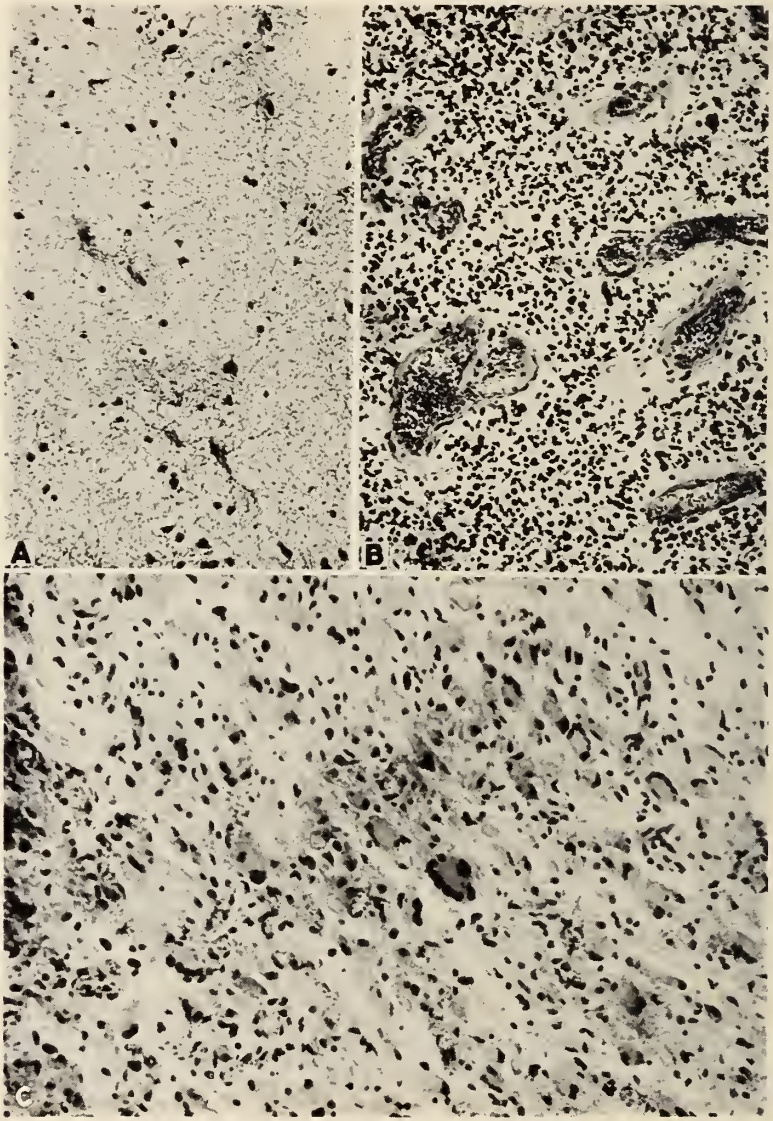


FIG. 5. A. The histologic appearance of tumor tissue obtained at first operation in case 1.

B. The histologic appearance of tumor tissue obtained at second operation in case 1. It now has the character of transitional glioma.

C. The histologic appearance of tumor tissue obtained at third operation in case 1. The giant cells are those usually found in spongioblastoma multiforme.

Examination. There was left sided hemiparesis, including the face; left hemi-hypesthesia, also including the face; increased deep reflexes on the left side; diminished

abdominal reflexes on the left side; equivocal Babinski sign on the left side (with a frank Babinski sign on the right side); exhaustible ankle clonus on the left side; astereognosis on the left side; bilateral papilledema; somewhat contracted visual fields more marked in the left temporal area.

Course. The diagnosis of a cerebral neoplasm in the right post central area was made and a craniotomy with partial extirpation of the tumor in the right parietal lobe was carried out.

The Pathological Report (S-33901) on biopsied material was as follows: Large area of gliosis (not unlike the type occuring in degenerative processes (fig. 5a)). Many vessels with adventitial infiltration. Infiltrating cells mainly mononuclear in type, although a few polymorphonuclear leucocytes are also seen. Character of the infiltrations are like those seen in degenerative or neoplastic lesions.

Recovery from the operation was uneventful. Power began to return in the upper left extremity. The papilledema, however, still persisted and the bone flap remained elevated. Severe headache persisted and a generalized convulsion took place.

Five weeks after the first operation, a second exploration was done. The surgeon found softened brain tissue and some fluid but no frank evidence of tumor. He concluded that all of the tumor had been removed at the previous operation. Fragments of the softened tissue was removed and sent to the laboratory for examination.

The pathological report (S-37346) read as follows: Fragments of a highly cellular gliogenous tumor. It is very vascular and contains a few islands of spongioblastic tissue (fig. 5b).

Following the second operation, improvement slowly took place. Power returned, headaches diminished and the patient was able to walk. Meanwhile deep x-ray treatment was given, but the papilledema persisted and the bone flap continued to elevate.

Following a severe convulsive seizure involving the left side of the body, he was returned to the hospital, twenty-one months after his second craniotomy. He was in a state of semi-stupor. There was a large cerebral hernia, and left hemiplegia. On his second day in the hospital, an extensive resection of the tumor was carried out by means of electric cautery. A very satisfactory and, possibly, complete removal of the tumor was thought to have been accomplished.

Pathological report of the specimen removed at this operation read as follows: "Section shows a densely cellular neoplasm which is fairly vascular. The striking feature of the tumor is the large number of spongioblasts and multinucleated giant cells (fig. 5c). The meninges show thickening and dense infiltration with lymphocytes. Diagnosis: Spongioblastoma."

A brief period of marked improvement in the patient's general condition followed the operation, but on the eighth postoperative day, his temperature suddenly rose to 104°F. A wound infection and cerebrospinal fluid leak from the wound were noted. Gradually, headache and vomiting reappeared. A gradual decline was followed by death.

Comment. A reexamination of the section of the tumor, removed at the first operation, shows it to be a benign astrocytoma. The infiltrations referred to were correctly interpreted as reactive in character, for such infiltrations are common in gliogenous and particularly, glioneuromatous tumors of the brain. It was the acellular character of the lesion, which left some doubt in the mind of the examiner when the tissue was first studied, but its neoplastic character was established by the later observations. Months later, another tumor mass from the same location was

removed. Its histologic character showed a distinct departure from the structure of the tumor mass removed at the first operation. At this time there was found a densely cellular mass, with the cell organization regarded as characteristic of transitional form of glioma. The histologic appearance of the tumor removed at the third operation, of course, indicates further progression in the line of acquisition of malignant features such as seen in spongioblastoma multiforme.

The progressive alterations in the histologic character of the tumor were obviously in the direction of the less differentiated, and hence more malignant form.

Case 2. *Signs of increased intracranial tension, but no frank picture of brain tumor; sinuses explored; improvement; recurrence of symptoms now more definitely pointing to brain tumor; craniotomy; glioma; recurrence; transitional glioma; decline; necropsy; spongioblastoma.*

History. D. M. a man, aged 33 years, suddenly began to experience severe headache and to vomit. At the end of two weeks, these symptoms became more pronounced and he was frequently overcome by drowsiness. He was treated for a probable acute sinus infection and showed, at first, moderate improvement. More severe headaches then set in. A roentgen-ray examination revealed moderate clouding of the frontal sinuses and bilateral optic neuritis was present. Though nasal examination revealed no positive findings, a sphenectomy and an ethmoidectomy were performed, giving the patient some relief from headache. One week later, forceful vomiting, dizziness and intense headache brought him for reexamination and advancing papilledema was now disclosed. An expanding intracranial lesion was then suspected and he was admitted to the hospital eight weeks after the onset of the early symptoms.

Examination. There was slight weakness of the right upper and lower extremities, slight right supranuclear facial weakness, bilateral papilledema with retinal hemorrhages, and clumsiness in performing skilled movements with the right upper extremity and depressed deep reflexes. The right knee jerk was more active than the left.

Course. The diagnosis of an expanding neoplastic intracranial lesion in the left cerebral hemisphere was made. Encephalography was performed and shifting of the ventricular system to the right was noted. A craniotomy with exposure of the temporal lobe revealed a yellowish hue of the cortex and in one area the tissue appeared somewhat softened; but no frank tumor could be seen by the naked eye. By means of the aspiration needle, some tissue was removed for anatomical study.

The pathological report (S-37072) read as follows: "Fragments of brain tissue probably derived from a glioma" (fig. 6a).

Following the operation, the patient developed an incomplete aphasia and right hemiparesis. The aphasia was of the motor type. While the aphasia improved slightly, the papilledema and complaints of headache continued. Deep x-ray therapy was administered. This was followed at first by improvement, evidenced by further recovery of speech, the return of power in the right arm and leg, and the disappearance of headache. The patient returned home, and there began to manifest an increasing number of generalized convulsions. Severe headaches returned, the papilledema likewise increased and retinal hemorrhages appeared.

Second Admission. He was readmitted to the hospital four months after the

first operation. Examination at this time showed marked motor weakness of the right side of the body including the right face, bulging of the osteoplastic flap, and impairment of sensation on the right side of the body. There was a mixed motor and sensory aphasia and the bilateral papilledema reached four to five diopters. The deep reflexes were increased on the right side and there was a Babinski sign on the same side. On the tenth day in the hospital, a flap was again turned down, and some brain tissue was excised.

Pathological Report (S-37941). Fragments of brain tissue with areas of necrosis and islands of cellular infiltration. The cells are most likely gliogenous in character. There are several large cells suggesting the morphology of spongioblasts. The impression is gained that tissue is in direct proximity of a gliogenous neoplasm, probably spongioblastoma (fig. 6b).

The patient declined steadily following this operation. Further radiotherapy was considered unfeasible because of the patient's condition, and gradual decline was followed by death.

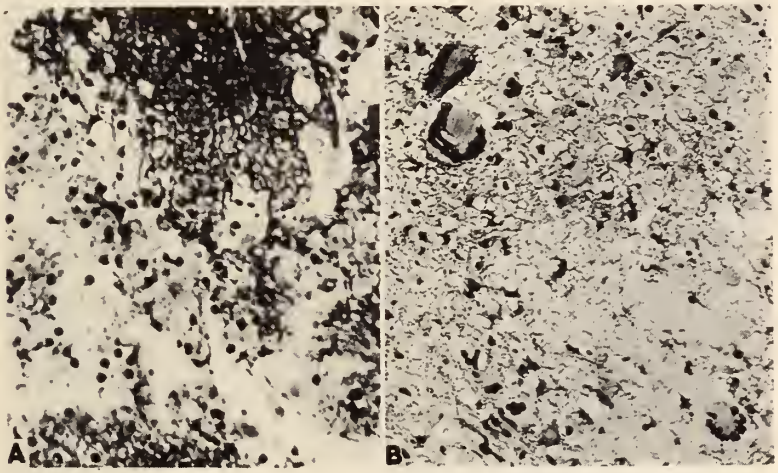


FIG. 6. A. The histologic appearance of tumor tissue obtained at first operation in case 2.

B. The histologic appearance of tumor tissue obtained at second operation in case 2.

Necropsy Findings. A large, soft, friable vascular tumor was found in the left hemisphere. It occupied almost the entire frontal and parietal lobes. Its histological character was typical of a spongioblastoma multiforme.

Comment. Here the histologic pictures presented by the tumor tissue removed at the different times, again showed the gradual transition of the tumor structure from a benign into a malignant form.

Case 3. *Gradual evolution of symptoms of brain tumor; craniotomy; transitional glioma found; recurrence; second craniotomy; spongioblastoma enucleated.*

History. M. O. a man, aged 41 years, suddenly passed through an epileptiform seizure, accompanied by a brief period of unconsciousness. Following this seizure,

he developed weakness of the left side of his face, which gradually increased. A few weeks later, he had two more epileptiform attacks. During the three days before admission to the hospital one year after the first epileptiform attack, he had several similar seizures. He gradually developed weakness in the left arm. His speech became very slow and his memory became impaired. He complained of declining eyesight and of a constant headache over his right parietal region.

Examination. There was early bilateral papilledema, a left hemiparesis including the face, bilateral pyramidal tract signs (left greater than right), intention tremor in the left upper extremity, and tenderness over the right fronto-parietal region of the skull.

Course. A neoplasm in the right frontal lobe was diagnosed, and a right craniotomy was performed. A tumor was found in the right frontal and parietal lobes.

The pathologic report (S-35815) read as follows: Transitional form of gliogenous tumor with spongioblastic islands distributed through a fairly cellular neuroglial field (fig. 7a).

The patient made an uneventful recovery and left the hospital. He walked slowly but without rigidity or ataxia. There was no gross impairment of the major muscle groups; but there was still moderate papilledema (O.D. 1.5; O.S. 1), and a left facial weakness. He was given x-ray therapy.

Second Admission. He returned to the hospital seven months later, because of the recurrence of the epileptiform attacks. At first, these attacks were rather infrequent but for the last three weeks they had become quite numerous so that during the last few days he had them repeatedly. They were of two kinds: 1) Brief episodes of motor aphasia, when the patient understood spoken language, but was unable to answer; and 2) Jacksonian attacks characterized by shaking of the head and tremor of the left hand. Both forms were associated with loss of consciousness.

Re-examination. He displayed a left central facial weakness; weakness and atrophy of the left upper extremity; a left sided hyperreflexia. There was no papilledema.

Course. The diagnosis of a recurrent tumor was made and a second craniotomy was performed with what was thought to be a complete extirpation of the tumor.

The pathological report (S-37181) read as follows: Section of the tumor shows features of malignant gliogenous growth. There are vast numbers of multinucleated giant cells of elliptical and irregular shape. There is a striking accumulation of glia cells and mononuclear leucocytes around the blood vessels. Diagnosis: Spongioblastoma (fig. 7b).

The patient failed to improve and went into a condition of status epilepticus, with attacks occurring every ten minutes, and lasting several minutes at a time. A third operation was performed, but the patient failed to rally and died.

Necropsy Findings. Little of the brain tumor was found at autopsy. A large defect in the right fronto-parietal region was found lined by softened tissue. The latter, on microscopic study, revealed the structure typical of spongioblastoma multiforme (fig. 7c).

Comment. The only difference between this case and Cases 3 and 4 is that the original tumor showed a slightly more cellular structure.

Case 4. *Two months' history of cerebral symptoms; craniotomy and removal of a soft tumor in the left temporal lobe; roentgen therapy; complete recovery; well twenty-six months later; recurrence and removal of the recurrent tumor; recovery; third recurrence; death.*

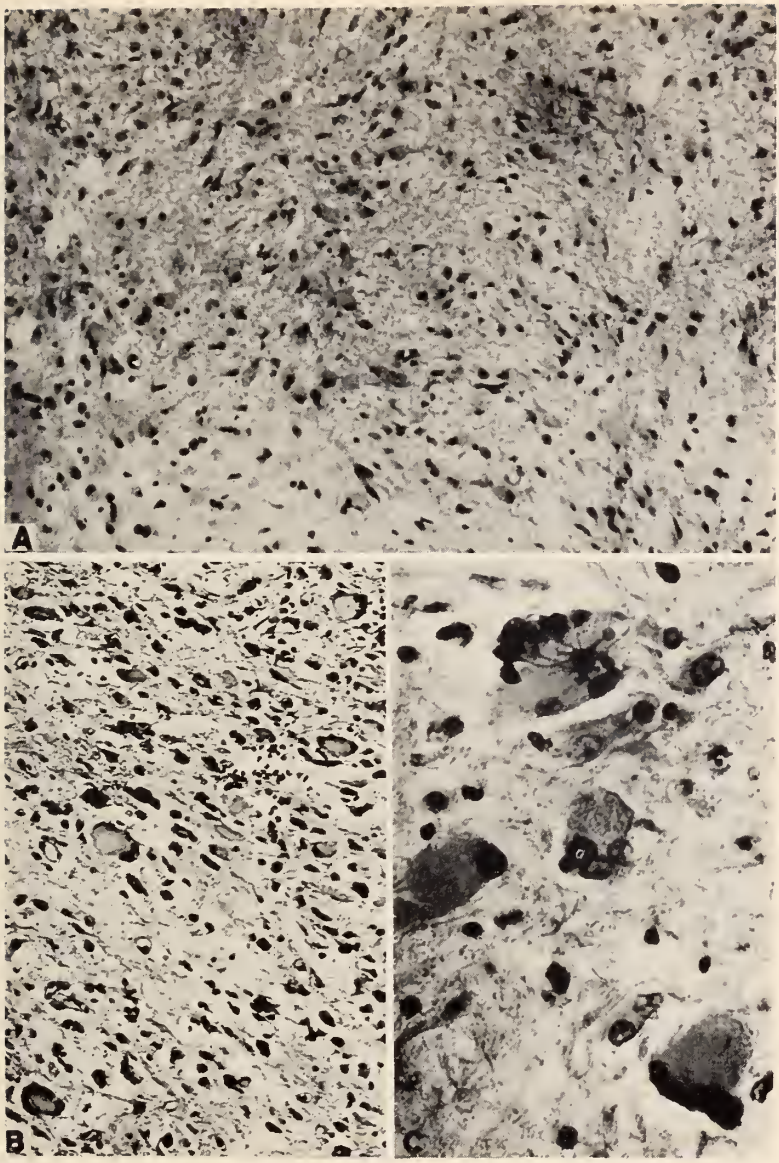


FIG. 7. A. The histologic appearance of tumor tissue obtained at first operation in case 3.

B. The histologic appearance of tumor tissue obtained at second operation in case 3.

C. The histologic appearance of tumor tissue obtained at autopsy in case 3.

History. N. A., a man, aged 33 years, had headaches over a period of eight months. These grew in severity and were accompanied, for several weeks, by attacks of dizziness and nausea. He then noticed difficulty in naming objects, and shortly thereafter became drowsy and disoriented.

Examination. The patient seemed dazed; in the more lucid moments he appeared euphoric. His pupils were unequal, and both somewhat dilated. There was bilateral papilledema of three diopters; slight right facial weakness, supranuclear in type; distinct weakness of the right upper and lower extremities. The tendon reflexes were diminished on the right, but ankle clonus and a Babinski sign were present. There was a mixed form of aphasia. The neck was distinctly rigid and there was tenderness on percussion of the skull over the temporal region on the left side.

Course. A cerebral neoplasm was diagnosed and localized on the left side and a left osteoplastic flap was turned down (Elsberg). A tumor of jelly-like consistency extending deeply into the temporal lobe was found. A large quantity of tumor tissue was removed by suction. The bone flap was replaced and the wound closed. Recovery from the operation was uneventful. The disturbances in speech cleared up rapidly; the reflexes became equal on the two sides, and the papilledema disappeared at the time when the patient was discharged from the hospital four weeks after the operation. For a number of months, he received deep x-ray therapy. Except for emotional outbursts, he was well and free from symptoms more than two years after the operation.

Pathologic Report (S-1069). The histologic picture was that of a spongioblastoma multiforme, characterized by the presence of many spongioblasts aggregated with fairly extensive islands surrounded by wide vascular channels. Glia cells of a more differentiated type alternated with the prominent giant-like spongioblasts (fig. 8a).

Second Admission. In the month of September, 1928, the patient returned with a recurrence of his symptoms: papilledema, aphasia, hemiparesis. Revision of the operation and the removal of much tumor tissue by suction was followed by the disappearance of the neurologic disturbances. Examination of the tissue removed at operation again showed it to be a spongioblastic growth (fig. 8b), but its cellular make-up indicated further progression in the direction of malignancy.

Comment. Following the second operation, the patient remained in satisfactory condition for a period of one year. Then with a recurrence of symptoms, a third operation was performed. Tissue removed at this time presented an alteration in the histologic structure. Here the large cells assumed elongated shapes, forms which are considered by some as less differentiated spongioblasts (fig. 8c). The term spongioblastoma unipolare was suggested for tumors consisting of cells of this type. I can not enter into the discussion of the propriety and adaptability of this term, but it is probably true that in this instance, we are dealing with further dedifferentiation of the growth.

Case 5. *Gradual evolution of signs of brain tumor; repeated craniotomies with progressive transition of the tumor into the malignant form.*

History. T. B., a woman, aged 37 years. Four years prior to her first admission to The Mount Sinai Hospital she passed through an abrupt epileptiform seizure. It was accompanied by loss of speech and was followed by loss of consciousness. In the course of time, other similar episodes occurred, during which a forceful turning of the head was an added feature. The attacks increased in frequency and there appeared a constantly increasing headache. When seen by a neurologist, advanced bilateral papilledema was discovered and she was referred to the hospital with the diagnosis of cerebral neoplasm.

Examination. There was bilateral papilledema, slight left facial weakness, generalized hyperreflexia, bilateral ankle clonus, bilateral Babinski sign, retarded cerebration and Jacosity.

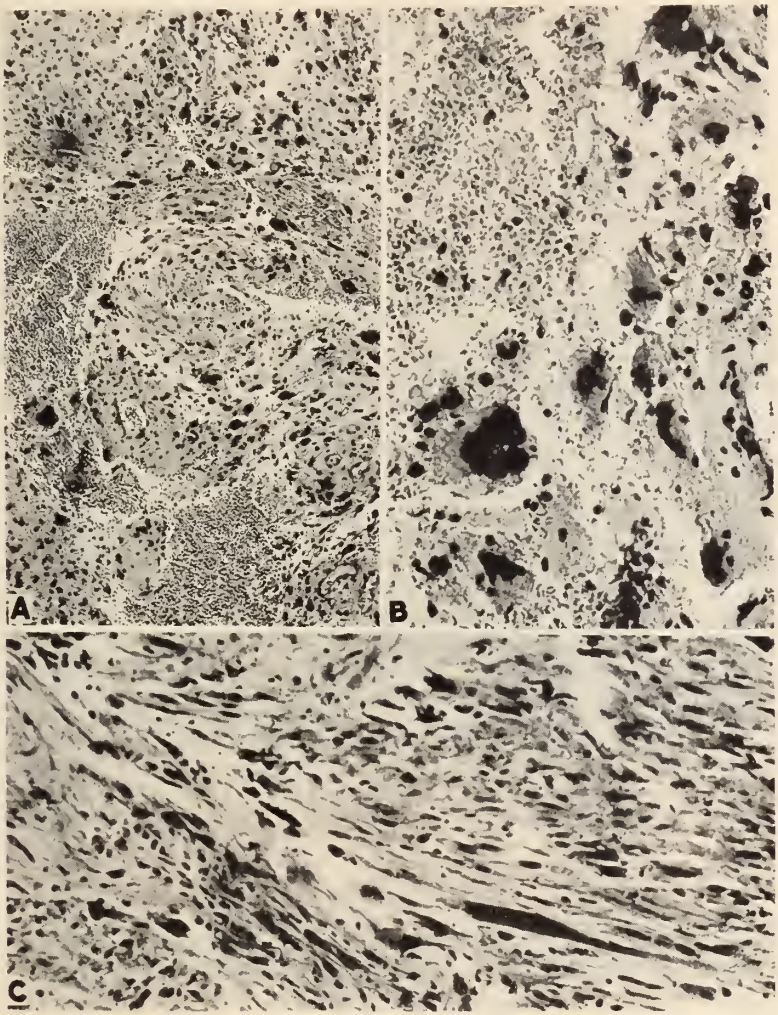


FIG. 8. A. The histologic appearance of tumor tissue obtained at first operation in case 4.

B. The histologic appearance of tumor tissue obtained at second operation in case 4.

C. The histologic appearance of tumor tissue obtained at third operation in case 4.

Course. A diagnosis of a neoplasm in the left precentral area of the frontal lobe or in the temporal lobe was made. An exploratory craniotomy was performed and a large part of a tumor in the left frontal lobe was removed.

Microscopic Anatomy of the Tumor. The pathologic report (S-47942) read as

follows: The tumor presents features of a transitional glioma, with many astroeytes dominating the field (fig. 9a).

Sccond Admission (18 months after diseharge). The patient remained free of symptoms for about fourteen months, and then headaehe aeeompanied by nausea reappeared in inereasing frequency and intensity. She began to show some intelleetual and personality alterations. The field of deeompression was bulging, there was slight blurring of the margins of the dises, flattening of the right side of the faee, slight weakness of the right upper extremity, increase in the deep reflexes on the right side and a Babinski sign on the same side. Revision of operation was thought inadvisable at this time and radiotherapy was relied upon to arrest further extension of the lesion. She returned home.

Third Admission. She remained at home but five days, when intense headaehe and semi-stupor neeessitated her return to the hospital. She was operated upon

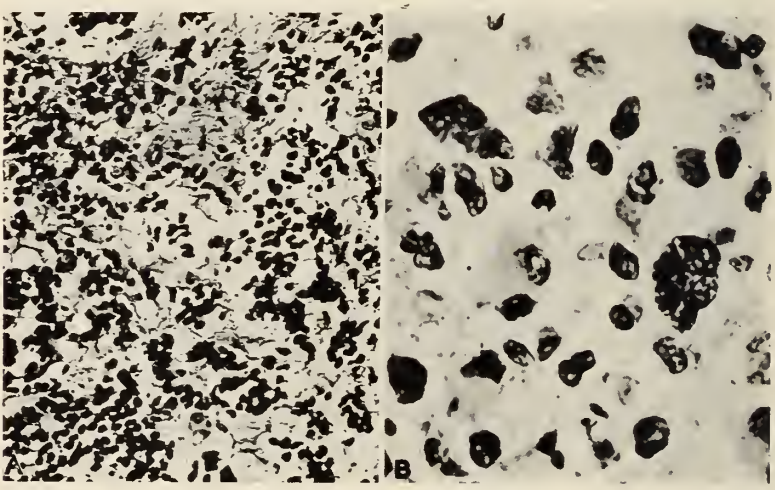


Fig. 9. A. The histologic appearanee of tumor tissue obtained at first operation in ease 5.

B. The histologie appearanee of tumor tissue obtained at third operation in ease 5.

and a large tumor was removed in "toto." A mieroscopie examination (S-66340) of this tumor showed it to be a typieal spongioblastoma multiforme (fig. 9b).

She passed through a stormy eonvaleseenee, but finally left the hospital with but a mild hemiplegia. She was again given intensive x-ray therapy.

Fourth Admission. She remained free of symptoms now for a period of six months. At about the end of this period she suddenly began to vomit and passed through a series of eonvulsive seizures affeeting the right side. When brought to the hospital, she revealed little new, but in view of the Jaeksonian attaek, revision of the operative field was eonsidered advisable. A large amount of neoplastie tissue was again diselosed and removed. Reeovery was stormy with transient aphasia and temporary hemiplegia. The patient was diseharged in good condition.

Microscopic Anatomy. In the pathologie report, the tumor was identified as a spongioblastoma.

Fifth Admission. The patient displayed mild mental ehanges and oeeasional speeeh difficulties, being at times unable to find a desired word. She was left with

a mild right hemiparesis. She returned to the hospital at the advice of the Follow-Up Clinic, but was allowed to go home in the belief that surgically, little could be accomplished now. She was referred for deep x-ray treatment.

Sixth Admission. She continued to complain of headache which seemed to have localized in the operative field. This continued for about a year, at the end of which time she began to display marked difficulty in speech and was readmitted to the hospital in April, 1939. She was found to be mentally slow. The nasal margins of the discs were blurred. There were pyramidal tract signs on the right side. She was again subjected to craniotomy and a cystic tumor was found in the right fronto-parietal region. The tumor was well demarcated on the surface, but infiltrating in the depths. It was thought that a fairly complete removal had been accomplished. At first there was complete loss of speech, but within a day speech began to return and there was steady improvement in the course of the next three weeks.

Microscopic Anatomy. The pathological report read as follows: Sections of the surgical material were stained with hematoxylin and eosin, toluidine blue (Nissl), silver and gold. The tissue is richly cellular and vascular tumor tissue and there are extensive extravasations of red blood cells. The tumor cells are distributed in an interlacing fibrous meshwork. Many cells are undifferentiated and often occur singly or in groups, enclosed by the meshwork. More differentiated cells contribute processes to the reticulum or direct them to nearby blood vessels. In the Nissl preparation, neuroblasts were found in large groups. Their cytoplasm usually stained in a granular fashion. Often they were found near blood vessels. Occasional multinucleated giant cells were seen containing neuroblastic nuclei.

Another type of nucleus, large round to oval in outline, showing a uniform, often coarse, stippling apparently belonged to spongioblastic cells. Frequently two such nuclei were encountered in a single large round cell with abundant clear-staining cytoplasm. Multinucleated giant cells with scanty cytoplasm were also present.

Rosette formations were occasionally seen in the preparations. In silver stains there were occasional small areas of liquefaction. Diagnosis: Neurospongioblastoma.

Seventh Admission. She returned to the hospital in January, 1940, seven years after her first operation complaining of increased difficulty in expressing herself and recurrent convulsive seizures. When examined she appeared to be euphoric, mildly aphasic with a right hemiparesis. The convulsive seizures were observed on the wards and they involved the right more than the left side. A craniotomy was performed on February 9, 1940 and a cystic tumor in the left premotor area was found and removed.

Pathologic Report (S-69513). The histologic structure of the tumor was reported as follows: Gross description: The surgical material consists of one large mass of several fragments of fleshy reddish discolored tissue totalling 45 gms. in weight. The large mass is of irregular shape and varying consistency, but is essentially cystic-like on palpation. It measures 10 x 5 x 3 cm. In a separate container, there is a triangular portion of firm discolored white tissue about 4 x 5 sq. cm. in size and 2 to 3 mm. thick. It resembles dura.

Microscopic description: Sections of the tumor and dura have been stained with hematoxylin and eosin, Van Gieson, Bielschowsky, Hortega variants I and II and the Nissl method. The tumor is composed of dense accumulations of cells, arranged in large groups separated by septa of connective tissue (stained by the Van Gieson method) (fig. 10a). The tumor cells contain large deeply staining nuclei with a very small amount of cytoplasm. Some of the cells contain deeply staining cytoplasm arranged in a triangular shape and these cells have larger nuclei which are paler and contain dense nucleoli (fig. 10b). Many mitotic figures are present. Large areas of necrosis and hemorrhage are found in the tumor. The dura is mark-

edly thickened and contains a small cyst-like space on its inner margin in the wall of which tumor cells may be noted. Diagnosis: Spongioneuroblastoma with neuroblasts predominating.

Comment. In this instance, there is evidence that the tumor existed for at least four years prior to the patient's first admission to the hospital. It is very probable that in the four years it had undergone some histologic change, so that the tissue removed at the first operation already presented the features of a transitional glioma. With each new operation the tissue disclosed further change toward a more malignant character, and finally, on the seventh admission to the hospital, not only was there evidence of massive recurrence, but it was also noted that the tumor had acquired the

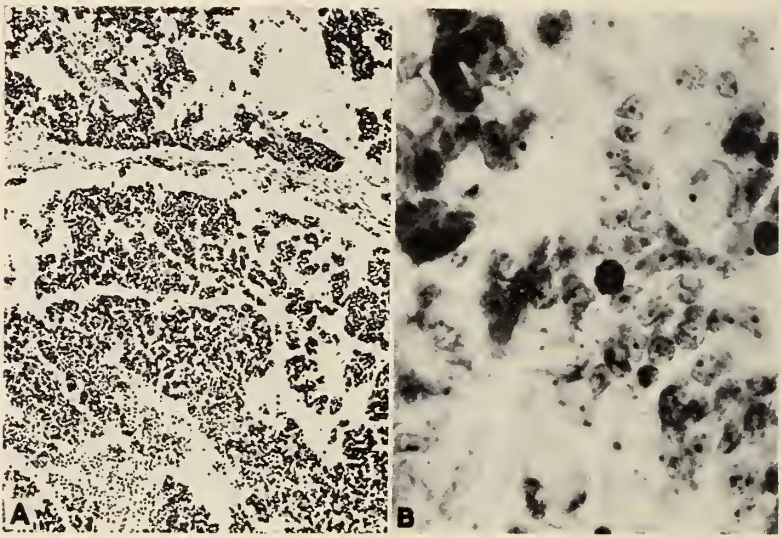


FIG. 10. A. The histologic appearance of tumor tissue obtained at fifth operation (seventh admission to the hospital) in case 5.
B. The same as in figure 10A under higher magnification.

character of a neurospongioblastoma. A glance at table 1 will show that such a tumor is low in the scale of differentiation of its component elements, represented by the spongioblasts and neuroblasts, hence the term spongioneuroblastoma.

DISCUSSION

An attempt is made in the introduction to familiarize the reader with the modern classification of primary neuroectodermal tumors of the nervous system, as applied particularly to brain tumors. The terms glioma, transitional glioma and spongioblastoma as well as glioneuroma, transitional glioneuroma and spongioneuroblastoma are introduced and their justification discussed. All this is done in order to provide the

morphologic ground or an explanation for the views offered as to the transition of the benign primary brain tumor into malignant forms.

Some observations on such occurrences already have been recorded in the literature. Tooth (8) reported two cases in which recurrences of the tumors which on first removal were apparently benign demanded a second operation and second excision of tumor tissue when alterations indicating a progressive transition into a malignant form was noted. His estimate of this phenomenon, he expressed in the following lines: "If these appearances are to be accepted, and I offer them with diffidence, one is forced to refer, on pathological grounds, that surgical interference, exploration or manipulation, with a few notable exceptions, is liable to awaken into greater activity a tendency to exuberance which, perhaps, may be almost latent at the time."

The above lines indicate that the observer accepted the probability that an anatomically benign tumor may at times assume a malignant character. He goes still further by postulating on the probability that the clinical activity of malignant tumors may be provoked by surgical interference. A critical review of the postoperative results in the material herein presented would tend to show that the progress manifested in the histologic alterations, as well as in the clinical course were rather retarded than hastened by surgery. Questions may be raised as to what extent the intensive x-ray therapy influenced the postoperative events, whether the radiotherapy contributed its share in the retarding process, or served as the main factor in slowing up the process? The histologic observations on our material are too uncertain to provide a conclusive answer. The marked increase in the necrobiotic processes, the impaired staining reaction of a large number of cells, the change in the cell forms as noted by others, were also recorded in our material. However, the interpretation of such alterations, in the light of experiences with untreated tumors, is exceedingly difficult. For, necrobiotic changes are found in all forms of gliogenous tumors and particularly in the spongioblastoma type. The modification of cell types which are found in the material of the treated cases, are also noted in untreated malignant tumors. The disturbance in the staining reactions may be accounted for by the application of chemical agents often employed during the operative procedures, or by vascular disturbances common to rapidly growing tumors. Thus, it would seem that, as yet, we have no definite criteria which would enable us to say, without doubt, that deep x-ray therapy is a contributory or a determining factor in the modification of the anatomical character of gliogenous tumors.

CONCLUSIONS

1. Under the terms Spongioblastoma Multiforme and Spongioneuroblastoma are described highly cellular tumors, consisting of embryonal, incompletely differentiated glial and neural elements (spongioblasts,

neuroblasts), of numerous giant cells and of various rudimentary cellular formations.

2. Gliogenous brain tumors illustrating the probable transition of a benign glioma or glioneuroma into malignant spongioblastoma or spongioneuroblastoma are described.

3. This transition may be recognized by studying tumor tissue removed at repeated intervals in instances where recurrences of the growths demanded reoperation.

4. An attempt is made to explain the transition of a benign into a malignant tumor, by the aid of the Conheim-Ribbert embryonal rest theory.

5. The influence of radiotherapy on such transition is briefly discussed and considered to be of doubtful significance.

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SARCOMA IN FIBROMYOMA OF THE UTERUS

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The uterus in the human is an organ which regularly undergoes physiological changes throughout the reproductive life of the female. These physiological changes, if slightly exaggerated, may become pathological. Transitions to malignancy may also at times be observed in benign lesions of the uterus.

The human uterus, due to its ontogenesis, normally has many elements which are histologically unripe and of an embryonal nature. Cohnheim stressed the importance of embryonal rests as the basis of tumor development. This is particularly true of the uterus, which is a favorable site for the various types of tumor development. A variety of tumors may occur in the uterus, independently of each other, as pointed out by Oskar Frankl (2). In addition, a malignant tumor may arise within a benign one. Sarcoma, circumscribed within a fibromyoma of the uterus, is a striking example of such a pathological process.

In two cases, in which myomectomy was performed for a benign fibromyoma, the tumor proved to be sarcoma. The prolonged postoperative observation with the subsequent operative study of the completely extirpated uteri, make these cases an interesting pathological report.

CASE REPORT

Case I. History. Mrs. S. M., a 28 year old white married female was admitted to the hospital complaining of irregular profuse menstrual periods, intermenstrual spotting, weakness and loss of weight. Her family history was essentially negative. In her past history it was noted that she had rheumatic fever two years ago. Her menstrual history began at thirteen. Menses occurred irregularly every four to five weeks with a profuse flow for five days. For the past six months the periods were more profuse with clot formation. She had also noticed intermenstrual bleeding. Her last regular period occurred on December 15, 1930. She had had no leucorrhea and no intestinal or urinary symptoms.

Examination. The patient was a very anemic, undernourished and underweight young woman. A systolic murmur was heard at the apex of the heart. The lungs were normal. No abdominal masses or tenderness could be elicited. Gynecological examination revealed a normal vulva and vagina. The cervix was normal in appearance. The uterus was anteflexed and enlarged by a tumor in the posterior wall the size of a small orange. The entire uterus was about the size of an eight to ten weeks gravidity, freely movable and not tender. The left ovary was the size of a large orange, cystic, freely movable and not tender. The right ovary and tube, both parametria and the pelvis felt normal.

Laboratory Data. The blood examination showed a hemoglobin of 27 per cent,

red blood cells, 3,000,000, white blood cells 7,600, platelets 660,000, polynuclear leucocytes segmented 57 per cent, polynuclear staff 2.0 per cent, polynuclear eosinophiles 3.5 per cent, polynuclear basophiles 2.5 per cent, lymphocytes 30 per cent, monocytes 5 per cent, recticulocytes 3.2 per cent, normoblasts 2 per 100 white blood cells, marked lymphocytosis, moderate anisocytosis and poikilocytosis with numerous microcytes. The blood picture was that of a severe secondary anemia of a chlorotic type. The urine examination was normal. The preoperative diagnosis was fibromyoma of the uterus with left ovarian cyst.

Operation. Myomectomy and left salpingo-oophorectomy were performed on May 24, 1931. The operative findings were an intramural fibromyoma the size of a tangerine located in the posterior wall of the uterus and a left dermoid cyst of the ovary about the size of a large orange. The removal of the well-encapsulated fibroid was easily accomplished and gave no hint of its histological character. Pre- and

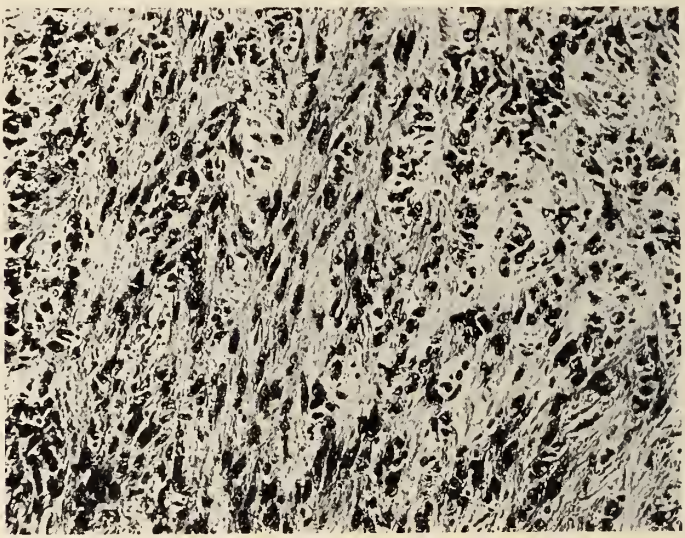

FIG. 1. Major portions of the fibromyoma are very cellular and the tumor cells are strikingly large and irregular. Their nuclei are atypical, large and hyperchromatic. There are numerous giant nuclei, some multinucleated. Occasionally distinct nucleoli can be seen. Mitotic figures are also present. Diagnosis—myosarcoma.

postoperative transfusions aided an uneventful postoperative course. The pathological diagnosis of the tumors was myosarcoma (fig. 1) and dermoid cyst of the left ovary. The patient was discharged from the hospital on the fourteenth postoperative day.

Course. Although the nature of the histological findings was explained, a radical operation or postoperative radiotherapy was refused by the patient and her husband. The patient was kept under close observation for six years for evidence of a local recurrence of the tumor. Her menstrual periods were regular and normal and she felt well. After three years absence from regular gynecologic examinations, she returned complaining of irregular prolonged menstrual periods for the preceding four months. The general physical examination was essentially negative. Gynecological examination showed a normal vulva and vagina and a normal cervix. The uterus was irregularly enlarged by several nodular tumors on its right and pos-

terior wall. The entire uterus was about the size of a ten to twelve weeks' gravidity. The right tube and ovary and both parametria felt normal. In view of the patient's

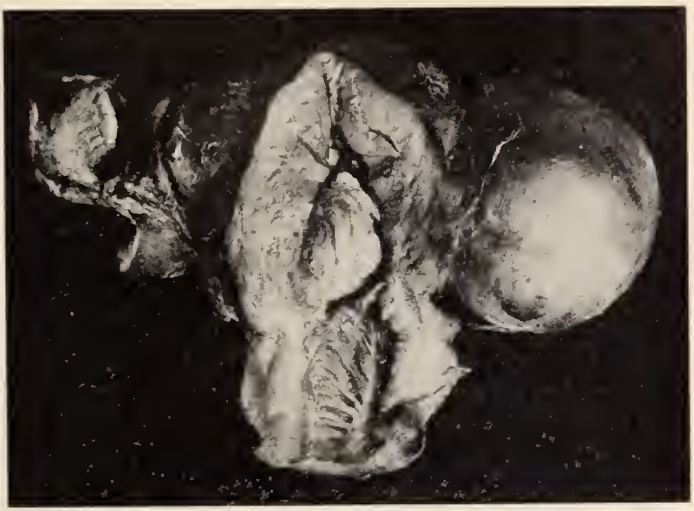

FIG. 2. Extirpated uterus and right Fallopian tube and ovary. The anterior uterine wall has been incised. The specimen shows multiple fibromyomata, one of them the size of a walnut situated submucously, and one the size of a small orange in the left uterine horn.

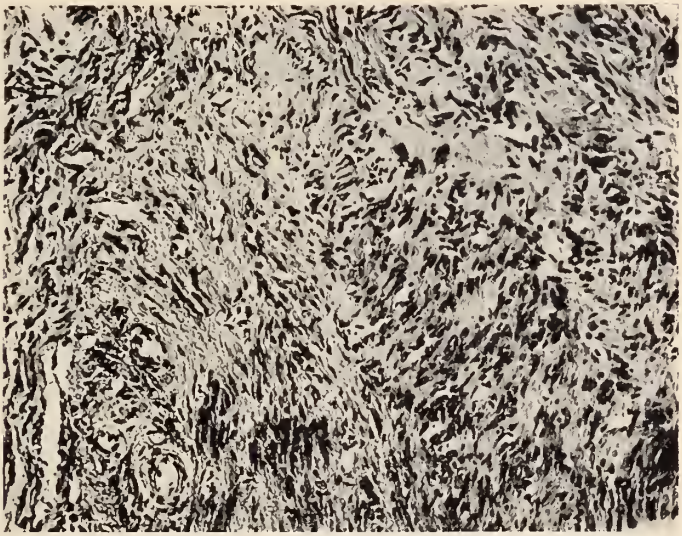

FIG. 3. A cellular fibromyoma, in contrast to the other fibromyomas in the same specimen which showed the usual histologic picture.

past history, the present symptoms and the gynecological findings, operative treatment was advised. At operation the uterus was found to correspond to the size, shape and involvement described preoperatively. Complete hysterectomy and

right salpingo-oophorectomy were performed (fig. 2). The postoperative course was uneventful and the patient left the hospital on the fourteenth postoperative

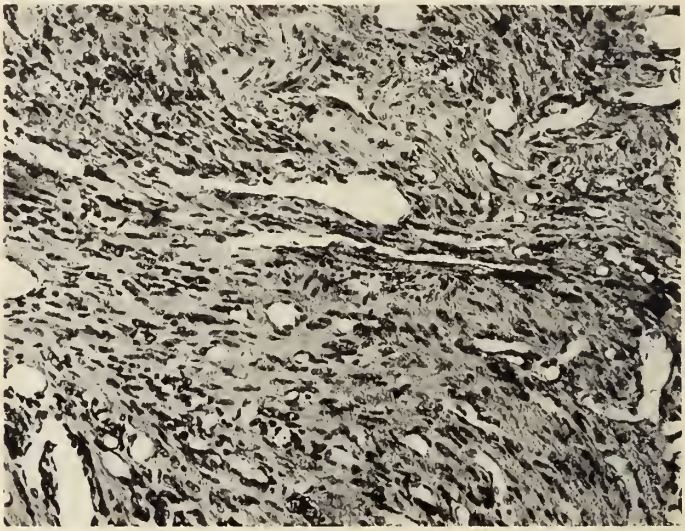

Fig. 4. Markedly cellular tumor with numerous large elongated irregular cells and giant nuclei. The nuclei show marked hyperchromatism. Invasion of lymph vessels is evident. Diagnosis—myosarcoma.

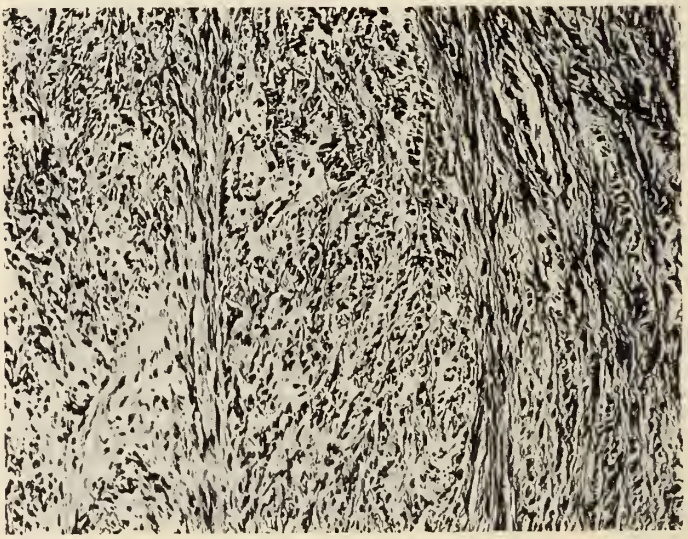

Fig. 5. A typical histologic picture of fibromyoma as found in all the tumors of the extirpated uterus.

day. The pathological diagnosis was multiple fibromyomas, and adenomyosis uteri with normal adnexa (fig. 3).

Case 2. History. Mrs. B. B., a 37 year old woman, had been married seven years. The family history was negative. Her past history included conservative treatment for irregular intermenstrual spotting for one year. Her menses began at thirteen years, were regular every twenty-eight days, lasting four to five days until one year before admission. Since then she had had intermenstrual bleeding and prolonged menstrual periods. There was no leucorrhea and no urinary or intestinal symptoms. Her chief complaint was menometrorrhagia for one year.

Examination. The general physical findings were essentially negative. Gynecological examination revealed a relaxed vulva and vagina with a normal cervix. The uterus was anteflexed, irregularly enlarged by multiple nodules varying in size from a pigeon's to a hen's egg. The entire uterus was the size of about a ten weeks gravidity, freely movable and not tender. The adnexae and parametria felt normal. The laboratory findings showed the blood and urine to be normal. A diagnosis of multiple fibroids was made.

Operation. In view of the local findings and the ineffectual conservative treatment for the symptoms, operative treatment was advised. Operation was performed June 27, 1934. The uterus was found to be enlarged by several intramural fibroids corresponding to the preoperative findings of the gynecological examination. The multiple intramural fibromyomata in the anterior wall of the uterus were removed by shelling them out of their distinct capsules. The convalescence was uneventful. The pathological diagnosis was myosarcoma (fig. 4). The patient was discharged on the fourteenth postoperative day.

This patient also refused further radical treatment as was indicated by the pathological findings.

Course. After a five year absence from New York, during which time she felt well and had normal menstrual periods, she returned for examination. She had been told by her physician in California that her uterus had increased in size during the past three months. She had no complaints but consulted her physician regularly for gynecological check-up as she had been advised. The general physical examination was essentially negative. Gynecological examination revealed an irregularly enlarged uterus fixed in an anterior position to the abdominal scar. The adnexae and parametria felt normal. In view of her past history and the above local findings a pan-hysterectomy was performed. The pathological diagnosis was multiple fibromyomas (fig. 5) and adenomyosis with no evidence of sarcoma. The postoperative course was uneventful and the patient left the hospital in good condition.

COMMENT

Sarcoma of the uterus was formerly regarded as an extremely rare tumor. With the routine histological examination of all postoperative specimens, it has been shown, according to the literature, to be more frequent than formerly suspected. The occurrence of sarcoma in fibromyoma is reported as varying from 1 per cent to 5 per cent, the average being 2.1 per cent. Geist (3, 4) found in a study of 250 cases of uterine and cervical fibromyomas, that 12 had sarcomatous changes of various types. This gave an incidence of 4.8 per cent. A review of 2916 cases of fibromyoma operated upon at The Mount Sinai Hospital from 1933 to 1940 showed 29 proven cases of sarcoma of the uterus, an incidence of 0.48 per cent. This is lower than that found in the literature, especially as every tumor removed at The Mount Sinai Hospital is subjected to thorough histological

study. The most frequent site of these tumors is in the uterine wall, while the greatest number of fibromyomas showing sarcoma are the submucous type, about 7 per cent; the smallest percentage is found in the subserous fibromyomas, about 1.6 per cent. Sarcoma of the uterus constitutes about 1.3 per cent of all uterine tumors and the ratio between corpus sarcoma and cervical sarcoma is about 8 to 1. The ratio between uterine carcinoma and uterine sarcoma is about 28 to 1.

Sarcoma of the uterus may occur at any age, but most cases are in or about the time of the menopause. Sarcoma in fibromyoma is usually found in younger women.

Sarcoma occurring in a fibromyoma may give no characteristic symptoms. In most cases described in the literature and in these reported, the operative indications were the symptoms usually seen in fibromyoma. Rapid growth of a myoma, a feeling of pelvic distention and pain from uterine contractions are highly suggestive symptoms of sarcoma in a fibromyoma. These symptoms are highly significant if they occur at the menopause or following x-ray treatment for fibroids. Cervical discharge and irregular uterine bleeding occur frequently when the sarcoma is submucous or endometrial in location. General systemic symptoms such as loss of weight, anemia and cachexia, do not occur often but when present ususally indicate extensive involvement. However, as in Case I, anemia and loss of weight occurred early, and could not be differentiated from the anemia and loss of weight due to menometrorrhagia of fibromyomas. Newton Evans (1) reported 72 cases of sarcoma of the uterus from the Mayo Clinic. These occurred in 4,000 cases of fibromyoma. All of these cases were diagnosed before operation as fibromyoma. This emphasizes the lack of any characteristic symptoms of sarcoma of the uterus, hence the difficulty of preoperative diagnosis. The positive diagnosis of sarcoma of the uterus is made in most instances by histological examination of the removed specimen.

The gross appearance of sarcoma occurring in fibromyoma may show no characteristic change and may resemble the tissue in which it is growing. In other cases, it may appear as a grayish-yellow, putty-like amorphous area instead of the glistening, hard, fibrillar cut surface of fibromyoma. Degenerative changes in sarcoma may produce irregular cavities and at times hemorrhagic areas may be seen. Sarcoma within a fibromyoma is usually located within the center of the benign tumor, but may also arise in the periphery of the fibroid and eventually involve the entire fibromyoma. Sarcoma of the uterine wall may also arise as a nodular growth and may simulate a sarcomatous myoma.

Histologically sarcomas are usually of a spindle cell, round cell or giant cell type, this classification being derived from the predominant cells. However, one rarely sees a pure example as the types are commonly mixed. Sarcoma cells may closely resemble the cells of their matrix. The sarcoma

may arise from muscle cells, connective tissue cells or from the cells of the blood vessel walls of the myometrium or of the uterine myoma. The cell form and its origin is manifest in the microscopic picture of the sarcoma. Robert Meyer (6, 7) emphasizes the above in order to classify sarcoma as follows:

1. Sarcoma myoglobicellulare (an unripe round cell myoblastic sarcoma).
2. Sarcoma myofusicellulare (a medium ripe spindle cell myoblastic sarcoma).
3. Sarcoma myocellulare (a ripe form of myoblastic sarcoma. This is also called leiomyoma malignum).
4. Sarcoma fibroglobicellulare (unripe fibroblastic sarcoma).
5. Sarcoma fibrofusicellulare (medium ripe fibroblastic sarcoma).
6. Sarcoma fibrocellulare (ripe fibroblastic sarcoma resembling connective tissue).

The myoblastic sarcomata are the most common forms which develop in fibromyomata.

Williams (11), Kelly and Cullen (5), and later Geist (4), Ogorek (8), and others accepted the theory of direct transition or metaplasia of muscle cells as the source of uterine sarcoma cells. Robert Meyer (6, 7), Oskar Frankl (2) and W. L. Strong (10) have claimed that the origin of uterine sarcoma from the fully differentiated muscle cells of the uterine wall or of the histologically differentiated elements of a myoma, does not fulfill all histogenic criteria. They maintain that the source of the sarcoma cells are myoblastic, fibroblastic or angioblastic rests within the myometrium or the fibromyoma. These unripe elements, if stimulated by as yet unknown causes, develop sarcoma. Frankl assumes that in the common mesenchymal origin for myoma and sarcoma, some elements mature first to form the myoma, while the immature elements within the myoma later develop sarcoma. These newer views of the histogenesis of sarcoma of the uterus tend to question the possibility of a metaplasia and eliminate the commonly accepted expression "malignant degeneration" of a benign tumor.

Sarcoma growing within a fibromyoma extends, as do the other forms of uterine sarcoma, by direct continuity and through the blood and lymph vessels. This explains the varied and distant types of metastases of sarcomas.

It is difficult to judge the efficacy of any one method of treatment of sarcoma of the uterus or sarcoma developed in a fibromyoma as the number of cases is relatively small; there is at present no unanimity in the classification of sarcoma according to the extent of involvement and histological characteristics; and there is no uniformity of therapeutic procedure.

Radiotherapy is one method of treatment. However, the merits of this form of therapy are still open to question unless the histological diagnosis shows the tumor to be of a radio-sensitive type. Surgical removal of a

sarcoma of the uterus by myomectomy, supravaginal hysterectomy or pan-hysterectomy with and without the removal of the adnexae, as well as the extreme radical operations such as the Wertheim or Schauta procedures, have been performed. The variety of operations emphasizes the difficulty in selecting the proper one. Theoretically a complete and radical operation should be performed in every case of sarcoma of the uterus if one keeps in mind the routes of sarcoma extension. However, the early removal of a sarcoma localized within a fibromyoma, such as was done in the two cases reported, has been sufficient to effect a cure.

The results of cure by operation are reported as 30 per cent five-year cures. Steinhardt (9) and Newton Evans (1) report respectively that 80 per cent to 100 per cent of their early operated cases remained well for five years or more. These statistics and the reported cases show the value of early operation. The early removal of a sarcoma localized within a fibromyoma may effect a permanent cure and could justify a revision of the prognosis and therapy of this type of sarcoma.

CONCLUSIONS

1. Two cases of uterine sarcoma within fibromyomas remained permanently cured after myomectomy.
2. The incidence of sarcoma within a myoma, from the statistics of The Mount Sinai Hospital, is much less than that reported in the literature.
3. Sarcoma in a fibromyoma gives no characteristic symptoms except when extensive involvement is present.
4. The histological classification of sarcoma is described according to morphology and genesis of the tumor.
5. Myomectomy, if performed in early cases, may effect a cure, while sarcoma of the uterine wall and of the endometrium requires radical operative removal.

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THROMBO-ANGIITIS AND RICKETTSIA—ETIOLOGIC RELATIONSHIP

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In 1895 there was admitted to The Mount Sinai Hospital a series of patients complaining of intense pain in the extremities and exhibiting symptoms of intermittent claudication. Some of them developed spontaneous gangrene which necessitated amputation.

Upon examination of the tissues, the pathologist concluded that the histological picture was that described by Winiwärter in 1879 as endarteritis obliterans, the cause of which was unknown.

In 1908 Buerger was making an intensive histological study of amputated limbs. As a result of his findings, he suggested that *thrombo-angiitis obliterans* described the disease more accurately. His observations, however, were made solely on Jewish patients, and he therefore concluded that the disease was one peculiar to the Jewish race.

The history of medicine reveals that diseases of undetermined etiology give rise to countless relief measures, but only when the cause is established can therapy be successful. Thrombo-angiitis obliterans, for example, has had many causes assigned to it, among them racial predisposition, the toxic effects of alcohol, tobacco, ergot, metabolic disturbances and syphilis.

The purpose of this paper is to record a series of observations which confirm the thesis I presented before the Medical Society of New York County in 1916—namely, that thrombo-angiitis obliterans is not due to any such causes, but is a late manifestation of typhus fever.

At that time, twenty-four years ago, my conviction was based on several salient facts. First, gangrene as a direct complication of typhus had been recorded by several authorities. Second, wherever typhus is endemic or widespread, there, too, we find a high incidence of thrombo-angiitis obliterans. To these significant facts I added two more, namely, the remarkable latency of virus remaining in the body after infectious disease, and the development of foci of bacterial activity long after the occurrence of the original infection. This observation has been supported by Zinsser, who, in 1934, expressed his belief that the virus of typhus may remain in the system for an indefinite period. It appeared to me, therefore, that thrombo-angiitis obliterans might be a late complication of typhus fever. Accordingly, I proceeded to study the pathological effects of typhus fever

upon the blood vessels and to attempt to isolate the causative agents of the disease from the blood vessels of thrombo-angiitis sufferers.

In 1917 the Hygienic Laboratories in Washington sent me guinea pigs, which had been inoculated with typhus virus. These and others, inoculated with blood from a case of Mexican typhus, were killed at the end of three and four months. Vascular thrombosis presenting features resembling those of thrombo-angiitis obliterans was discovered in the hind legs.

These findings are in accord with human pathological studies which show that typhus is primarily a disease of the endothelial cells of the blood vessels and that the histological changes in the blood vessels resemble those characteristic of thrombo-angiitis.

However, as the pathological picture is not exclusively typical of typhus but is associated with other diseases, the next step in order was to attempt the recovery of Rickettsia bodies from the affected blood vessels of thrombo-angiitis sufferers. This was done with the help of two pathologists.

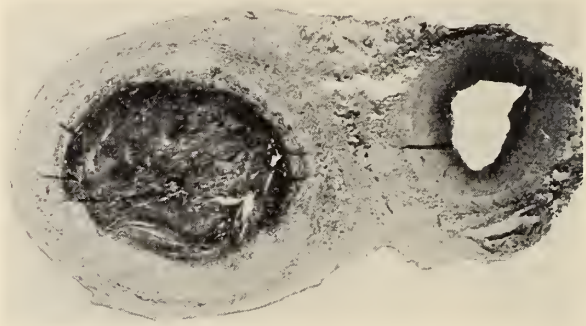

Fig. 1. Thrombo-angiitis-obliterans thrombosis

In 1923 each of them working independently found bodies morphologically similar to those described by Wolbach in his "Monograph on Typhus". They made no attempt to grow them, since no culture method existed at that time.

Thus, the validity of my hypothesis was confirmed by these important demonstrations, the occlusive thrombosis produced by typhus and the presence of what appeared to be Rickettsia bodies in the blood vessels of certain patients with thrombo-angiitis. To strengthen the hypothesis still further, a history or more certain evidence of typhus infection in every case of thrombo-angiitis obliterans had to be established. A history of such infection is, of course, not readily obtainable in every case. In the light of what we now know of typhus, the disease may occur in an abortive or non-apparent form with such mild manifestations that it is quite likely to escape diagnosis. In other words, while a positive history of typhus in a given case of thrombo-angiitis is significant, a negative history is without significance on this score.

It was necessary, then, to devise a means whereby a prior infection with Rickettsia could be established in cases of thrombo-angiitis. In 1934 I developed a cutaneous test for this purpose.

A few attempts to devise a skin test had been made by others. For example, in 1916 Jacobstahl made an extract from typhus-infected lice in which the virus was killed. Intracutaneous inoculation with the extract produced a positive reaction in acute cases of typhus fever, but the procedure was entirely too complicated to be of practical value.

Friedberger, Van der Reis and Delamare used small amounts of Proteus X19, but this test gave a positive reaction in typhoid fever and relapsing fever as well as typhus fever, hence it was of little diagnostic value.

While the agglutination test with Proteus X19 is now recognized as the means of establishing a definite diagnosis of Rickettsia infection, it may be positive for only thirty days and is usually negative after sixty days of convalescence.

Bogdanoff, Fleck and Nemschilov used a modified exanthin test which they claimed was specific for typhus during the first week. However, positive results were observed in healthy people, and in the convalescent period 80 per cent of the patients became negative in reaction. This test, therefore, could not take the place of the Weil-Felix reaction.

T. S. Sellers, Director of the Georgia State Laboratories, states that the incidence of reported cases of typhus fever increased from 5 in 1926 to 425 in 1935 and 1,035 in 1939 and he says that the Weil-Felix test has proved disappointing. He holds that the absence of typical clinical findings should cause the physician to be on his guard in the interpretation of the diagnostic significance of the Weil-Felix titers of a dilution less than 1:320. He and Dr. Henry Welch of the Connecticut State Laboratories, call attention to some of the difficulties of the Weil-Felix test and suggest means of avoiding them.

In 1935 Dr. Brodie and I published a preliminary report on a skin test for which we used a formalinized suspension of Rickettsia which was supplied us through the courtesy of Dr. Hans Zinsser of the Department of Bacteriology and Immunology of Harvard University.

In our skin test we injected intracutaneously 0.1 cc. of the vaccine on the palmar aspect of the forearm. As controls, a Proteus X19 filtrate and a formalinized suspension of tunica vaginalis from healthy guinea pigs were used, as well as suspensions of streptococci and staphylococci.

Three groups of individuals were tested: (a) Individuals convalescent and recovered from typhus fever or Brill's disease; (b) normal control individuals and (c) patients with thrombo-angiitis. Our first series consisted of twenty patients, all of whom had a history of Brill's disease six to eight years prior to the test, and in all but one case the diagnosis at that time had been confirmed by the Weil-Felix reaction.

An additional individual similarly tested during the second week of convalescence had a positive reaction 2 cm. in diameter.

For controls, twenty-two adults with no history of typhus were given similar tests. They were observed 24 to 48 hours after the injection. None of the controls gave any reaction. On the other hand, in tests given twenty adults with a history of previous typhus infection, all showed an erythematous indurated area from 1 to 4 cm. in diameter at the end of 24 hours.

These results suggest that patients who have recovered from typhus fever evince a sensitivity to Rickettsia bodies and that this sensitivity persists a considerable length of time.

The third group tested consisted of thirty-two patients suffering from thrombo-angiitis obliterans from one to sixteen years. They, too, gave positive reactions to our test.

Additional Tests. Through the courtesy of Dr. William H. Park and the assistance of Mr. George Stein, we were able to produce four separate preparations of vaccine. We inoculated guinea pigs and rats with a Rickettsia suspension and passed the cultures through several generations in order to obtain the maximum number of Rickettsia bodies.

For this purpose Dr. Karl Landsteiner of the Rockefeller Institute furnished us with a European tissue culture strain. It was passed through several generations of guinea pigs and a brain emulsion prepared. Another European vaccine used was prepared for us by Professor R. Weigl of Poland.

Dr. Zinsser supplied us with a Mexican strain from guinea pigs, and the vaccine was prepared according to the method suggested by Zinsser and Castaneda which afforded a greater yield of Rickettsia than the tissue culture, the chicken embryo culture or scrapings from the tunica vaginalis of the inoculated guinea pig.

We gave upward of 1,000 intracutaneous inoculations with the Rickettsia suspension and the various control materials.

The tests were made with these objects in view: (a) To see whether convalescent and recovered cases of Brill's disease exhibit a sensitivity to intradermal injections of Rickettsia-prowazeki; (b) to note whether a similar sensitivity is manifested in patients with thrombo-angiitis; (c) to discover whether the sensitivity is quantitative or qualitative and (d) to determine which suspensions are followed by the greatest number of positive reactions in cases of thrombo-angiitis and negative reactions in controls.

We found that the most satisfactory results were obtained with suspensions containing 120 to 170 million Rickettsia per cubic centimeter. Various strains of Rickettsia, capable of producing typhus fever in a man, have been isolated and their vectors recognized. The severity of the infection depends not only upon the degree of immunity of the individual affected but also upon the virulence of the infection. A striking example may be found in the Wyoming and Montana Rocky Mountain spotted

TABLE 1

965 skin tests with vaccines of various concentrations of rickettsia and controls

	ZINSSER 1	ZINSSER 2	ZINSSER 3	ZINSSER 3 HEATED	ZINSSER 3 1–4	ZINSSER 3 1–4 HEATED	ZINSSER 3 1–10	ZINSSER 140,000,000	PROTEUS X19 FILTRATE	TUNICA VAGINALIS	WEIGL EUROPEAN	WEIGL HEATED	WEIGL 1–4	WEIGL 1–4 HEATED	WEIGL 140,000,000	N.Y.U. 1	N.Y.U. 1 HEATED	N.Y.U. 170,000,000	N.Y.U. 150,000,000	N.Y.U. 120,000,000	N.Y.U. 100,000,000	N.Y.U. 2	N.Y.U. 150,000,000	N.Y.U. 140,000,000	N.Y.U. 100,000,000	N.Y.U. 3	N.Y.U. 150,000,000	N.Y.U. 140,000,000	N.Y.U. 100,000,000	EUROPEAN 1–10	STAPHYLOCOCCI	STREPTOCOCCI	N.Y.U. 1-2-3-POOLED
Thrombo-angiitis obliterans	12+	21+	9+ 1−	5+	9+ 2−	11+ 4−	7+ 8−		5−	19−	12+ 2−	1+	11+ 4−	29+ 4−	26+	7+ 1−	1+ 1−	34+ 3−	12+	25+ 1−	5+ 5−	6+ 2−	8+ 1−	12+ 1−	3+ 2−		8+	6+	1+	3+ 1−	5+ 7−	9+ 7−	
Typhus	25+	13+ 3−	13+ 2−	1+	9+ 2−	15+ 6−	3+ 4−	4+ 1−	5−	22−	13+ 2−	1+	17+ 4−	24+ 5−	9+ 1−	2+	2+ 1−	47+ 1−	3+	28+ 3−	1+ 2−	2+	6+	33+ 1−	2−		4+ 1−	10+ 6−		1−	3+ 4−	5+ 4−	4+
Controls	13− 1+	3−	2− 2+		5− 1+	24− 2+	7− 1+		3−	7−		3− 1+	10− 3+	14− 2+	14−	8− 1+	7− 7+	4− 2+	1+	8−	4−		6−	12− 1+			5−			7−	8− 3+	9−	2−

fever as contrasted with the eastern type of the fever. The former usually has a tremendous mortality, on the average, 70 per cent; occasionally, 100 per cent, whereas the eastern type has practically no fatality at all. Then, again, there is the European typhus fever in epidemic form with its

	WEIGL 140,000,000	N.Y.U. 1-2-3 140,000,000	ZINSSER 1-2-3
TYPHUS	9+ 89% 1-	121+ 90% 13-	42+ 93% 3-
CONTROLS	14- 100% 0+	31- 97% 1+	16- 93% 1+

FIG. 2. Results of skin tests with Weigl European vaccine concentrations 140,000,000 rickettsia to cubic centimeter. Results with three different New York University preparations of vaccine (Murine). Results obtained with three different vaccines (Murine) prepared by Zinsser.

	WEIGL 140,000,000	N.Y.U. 1-2-3 140,000,000	ZINSSER 1-2-3
THROMBO-ANGIITIS OBLITERANS	26+ 100% 0-	71+ 96% 3-	33+ 100% 0-
CONTROLS	14- 100% 0+	31- 97% 1+	16- 93% 1+

FIG. 3. Results of skin tests with Weigl European vaccine concentrations 140,000,000 rickettsia to cubic centimeter. Results with three different New York University preparations of vaccine (Murine). Results obtained with three different vaccines (Murine) prepared by Zinsser.

high mortality and the endemic or murine typhus with its comparatively low mortality. According to Zinsser, there is reason to believe that the series of cases reported by Brill in 1910 were recrudescences of supposedly European or epidemic typhus.

To resume, then, in 100 cases of Brill's disease which we used in our

investigation, 97 per cent had a positive skin reaction following the intracutaneous injection of the Rickettsia suspension. In 100 cases of thrombo-angiitis, 100 per cent gave a positive reaction. Similar tests proved negative in 93 per cent of a corresponding number of controls. In addition to presumably normal individuals, this group included persons with arteriosclerosis, diabetes (with and without gangrene), typhoid fever, pneumonia, scarlet fever, bacterial endocarditis, intestinal tuberculosis and other acute infectious conditions.

In the series of cases of Brill's disease, one gave a history of having had typhus three times, and eleven had it twice. These and fourteen others who had had typhus but once complained of chronic headaches and claudication.

An examination revealed that all twenty-six patients showed unmistakable signs of thrombo-angiitis, that is, low blood pressure, absence of

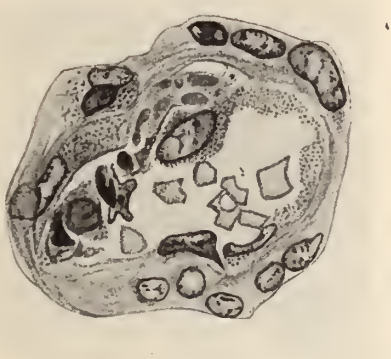

Fig. 4. Arteriole showing early typhus lesion, degeneration of the endothelium and beginning mural thrombus. The swollen endothelium contains many small rickettsia bodies. Autopsy on fourteenth day. 1200 diameters (Wolbach).

pulsation in one or both tibial arteries, coldness of the extremities and a noticeably diminished amplitude, as revealed by the comparative oscillometric estimation of the two extremities.

On the basis of the findings which have just been reviewed, I feel justified in making the statement that there is much substantial evidence linking typhus fever with thrombo-angiitis obliterans. Moreover, it is a source of great satisfaction to me that since 1916, when I first formulated the hypothesis of the relationship between thrombo-angiitis and typhus fever, others have come to share my belief that the former is infective in origin. For example, in October 1936 the Mayos reported the case of a surgeon who developed accidental thrombo-angiitis in his arm following an infection acquired while performing an amputation for thrombo-angiitis obliterans.

The same etiological relationship of thrombo-angiitis to typhus sug-

gested itself to Netter in 1932 and to Angelesco, Buzoiani, Troisier and Horowitz in 1933.

I need not elaborate on the significance of this theory. It establishes the etiology of the disease and so holds out to us the promise of prevention and effective treatment.

Additional proof of my theory is to be found in the similarity of the histological pictures presented by both conditions.

In 1939 Parker reported thrombo-angiitis obliterans as one of the complications following Rocky Mountain spotted fever and made mention

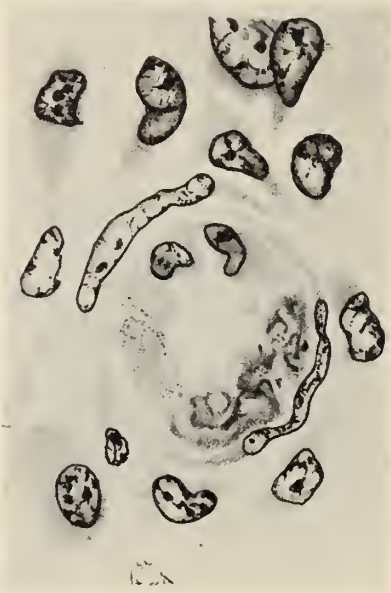

Fig. 5. Arteriole showing swollen degenerated endothelial cells and an early fibrin mural thrombus. Two endothelial cells contain rickettsia. There is an early perivascular reaction (endothelial leucocytes). Autopsy on the fourteenth day. 1800 diameters (Wolbach).

of the frequency with which gangrene of the extremities is observed in animals inoculated with the Rickettsia of this disease.

Gangrene as a complication or as an aftermath of typhus fever had also been noted by some of the earlier authors.

For example, back in the sixteenth century during an epidemic sweeping from Russia over the entire continent, including the British Isles, and causing millions of deaths, Jordanus described the outstanding symptoms of typhus as: high fever, prostration and gangrene.

Two American surgeons who had visited Russia during the epidemic which was devastating the country between 1921 and 1923 told me conditions were so serious that they were pressed into service and called upon

to perform almost two hundred major amputations within the brief period of six to eight weeks. These amputations were performed on cases of convalescent typhus fever.

In Japan the Rickettsia disease, *tsutsugamushi*, has been very prevalent. It is caused by the Rickettsia-infected mite infesting a small animal corresponding to our field mouse.

In 1913 Koge wrote that he was of the opinion that "juvenile gangrene" was more common in Japan than in any other country in the world. He ascribed the gangrene to an increase in the viscosity of the blood and suggested hypodermoclysis of Ringer's solution as a remedy.

In 1922 Wolbach noted in his report of exhaustive studies on typhus fever in Poland that Rickettsia bodies were found in the blood stream during the early manifestations of the disease and later became imbedded in the endothelium, causing proliferation and necrosis of the endothelium and inducing occlusive thrombosis. Some of the cells containing Rickettsia bodies penetrated the perivascular tissues as well as other layers of the vessels, the infiltration resulting in peri-angiitis. From his observations and those of others it may be concluded that the extent of the pathology observed in and about the blood vessels is dependent upon the virulence and duration of the infection.

In 1914 and again in 1915 Fraenkel described acute lesions of the blood vessels with thrombosis and a perivascular infiltration. The latter was largely comprised of accumulation of cells derived from the adventitia and peri-adventitia and also containing lymphocytes and polymorphonuclear leucocytes. He held these lesions to be specific for typhus.

Fraenkel's findings and conclusions were confirmed by Aschoff in 1915; Poindexter, Ceelen, Bauer, Kyrle, in 1916; Morametz and Herzog in 1918; Nichol in 1919 and several others. In 1920 Wolbach and Todd reported the same type of lesion in cases of Mexican typhus fever.

According to Wolbach, the vascular lesions and the perivascular accumulations are always present on or after the fifth day. The only other disease known to have a similar histological picture is Rocky Mountain spotted fever. The difference between the two conditions is a quantitative rather than a qualitative one. In Rocky Mountain spotted fever the destruction of the blood vessel walls is more extreme than in typhus, and the perivascular accumulations are less pronounced and do not form discrete tubercle-like nodules observed in the latter.

In its earliest stages, thrombus formation consists in accumulation of blood platelets massed upon and apparently within swollen endothelial cells *in situ*. The endothelial cells at the base of the thrombus frequently contain numbers of Rickettsia.

The more recent studies of Pinkerton suggest that the Rickettsia in typhus are cytoplasmic, while in Rocky Mountain spotted fever the Rickettsia are found in the nuclei of the endothelial cells. Pinkerton

emphasizes the tendency of the endothelium toward necrosis and periangiitis as characteristic of Rocky Mountain spotted fever. However, the studies and observations of European typhus made on *humans* by Wolbach, Bauer, Wiener, Jochmann and others indicate that the histological picture may be the same for this type of the disease.

In the course of our review we have implied that typhus is widespread.

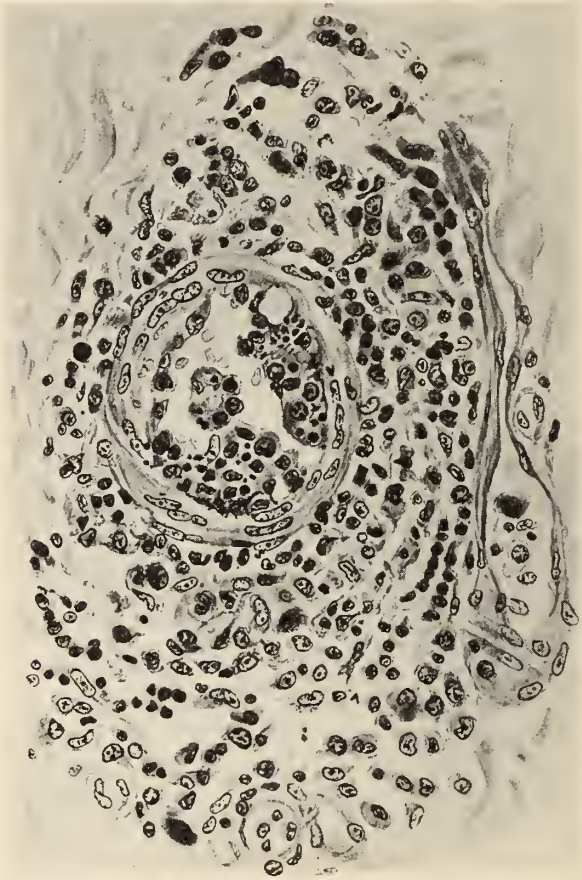

FIG. 6. Arteriole, death in second week. Shows attached mural thrombi composed almost wholly of phagocytic endothelial cells. There is an early proliferative perivascular reaction. 400 diameters (Wolbach).

It is, indeed, world-wide in distribution, and occurs in all climates and latitudes. It is accredited with a death toll equal to, if not greater than, any other infectious disease. Where there is typhus, there is thrombo-angiitis; where typhus is epidemic and endemic, thrombo-angiitis abounds.

It now remains for us to review other hypotheses which have been advanced to account for thrombo-angiitis obliterans. As mentioned before, thrombo-angiitis has had many causes ascribed to it, among

which are racial predisposition, toxic effects of alcohol, ergot and tobacco, metabolic disturbances and syphilis. None of these suggestions have proved to be the real cause of the disease, and all can readily be controverted.

It has been quite generally believed that thrombo-angiitis is peculiar to the Jewish race, largely because a number of years ago the majority of cases observed in this country occurred among poor Jewish immigrants from Russia and Poland. As a matter of fact, these people have been so scattered and intermarried, that a pure Jewish strain can scarcely be said to exist. To refute the racial hypothesis still further, in New York, where a relatively large number of Jews had been living, not a single case of thrombo-angiitis was reported until the influx of the immigrants from Russia and the Baltic States in the 1890's.

Friedman observed the disease among the Estonians and Russians as well as the Jews. In 1920 he stated that the disease appeared chiefly among Jews, because few Estonians and Russians had migrated to this country. Koukin reported a series of 70 Russian peasants, only 3 of whom were Jews. Schum stated that in Russia the disease is just as common among Gentiles as among Jews.

Meleney observed 25 cases in China. Ludlow saw over 100 cases in Korea, and in 1913 Koge spoke of the disease as being common in Japan. Non-Jewish patients are also reported in England, France, Spain, Africa, Turkey and elsewhere. Even more significant, perhaps, is the fact that Matas, Ochsner, Orr, Freeman and others report cases among American born individuals of non-Jewish parentage. In fact, prior to the large numbers of immigrants from Russia and Poland endarteritis obliterans, or thrombo-angiitis, was unknown here. Yet, we had had a large Jewish population here for many generations.

With regard to alcohol, it has been found that the arterial disease attributed to the toxic effects of this drug is not thrombo-angiitis.

Syphilis, too, may be excluded as an etiological factor, because the Wassermann reaction in these cases is usually negative.

Ergot poisoning is due to the overconsumption of diseased rye. There is no evidence that thrombo-angiitis obliterans is more common among individuals affected by ergot than among others. Surely this cause could not be operative in those parts of China where the staple diet is millet and rice, or in Japan where it is fish and rice.

The prevailing opinion that tobacco enters largely into the etiology of the disease does not appear to have a rational basis. Although many patients with thrombo-angiitis obliterans give a history of excessive smoking, in view of the tremendous increase in the consumption of tobacco in recent years, an increasing incidence of the disease would logically be expected. According to federal reports, the consumption of cigarettes in the United States during 1939 reached the enormous number of 175

billion. It is also important to note that in Russia and Southeastern Europe tobacco is a luxury beyond the means of poor peasants. According to Meleney and others, about 40 per cent have never made use of tobacco in any form.

At Beth Israel Hospital, under my supervision, metabolic tests made on persons with thrombo-angiitis obliterans gave results in no wise different from those obtained with the tests on subjects used as controls.

CONCLUSION

We have presented historical, epidemiological, histological, microbiological and serological evidence that typhus and thrombo-angiitis are definitely related.

In the light of this evidence, we may conclude that thrombo-angiitis obliterans is a late manifestation of a previous infection with epidemic or endemic typhus, whether that infection originated in this country or any other country.

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CARCINOMA OF THE ANUS TREATED BY RADIATION THERAPY

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In spite of its infrequent occurrence, cancer of the anus presents important points in differential diagnosis and in choice of therapeutic method to be employed. During the seven-year period of 1933 to 1940, five cases of verified anal cancer were seen at The Mount Sinai Hospital. During the same period, 529 cases of rectal and recto-sigmoidal cancer were admitted. The incidence of anal cancer in this group of lower bowel neoplasms was 0.84 per cent. Of the five anal cases, one was a basal cell carcinoma, and four were squamous cell carcinomas. The basal cell lesion was treated by excision and cauterization; the squamous cell cases were treated by Roentgen-therapy only.

Although a higher rate of incidence has been found by others (Buie (1), 1.73 per cent; Raiford (2), 2.8 per cent; Kaplan and Rubinfeld (3), 4.8 per cent), it is possible that certain rectal tumors which spread distally and possibly under the mucosa of the rectum were included. This may be the situation in Kaplan's series of eight cases, in which four were squamous cell and four adenocarcinomata. Fricke, who reported fifty-one cases from the Mayo Clinic, Raiford, and others, find that at least 90 per cent of the lesions are of the squamous cell type. This should be expected, because the anal canal is lined by squamous cells of epithelial origin, like skin. The rare anal adenocarcinoma may be accounted for by the presence of aberrant sweat glands. Undoubtedly, incorrect anatomical classification of lower bowel tumors may be due to the loose teaching that the anal canal begins at the lower border of the prostate. The length of the anal canal varies greatly; it is from 1.5 to 3 cm. long (average 2.5 cm.), and its internal boundary is the pectinate line. Variations in length of the canal may be accounted for by the age of patient; the tonicity of the sphincters; previous operations; the presence of hemorrhoids; fissures; fistulae or other pathological states. The designation, "cancer of the anus", should be limited to lesions arising internally, at or below the pectinate line, and externally, from the perianal skin where the walls of the anus come together in their normal state of apposition in the intranatal fold. ("Anal verge"—Batson).

There is no characteristic symptomatology differentiating anal cancer from certain benign lesions of the anus or tumors of the rectum. The diagnosis must be established by biopsy. The presence of lues, lymphogranulomata, or tuberculosis should not deter one from taking biopsies,

because these lesions may be found coexisting with anal cancer. Should biopsy show an adenocarcinoma, careful investigation under anaesthesia, if necessary, should be done to determine the exact site of origin and extent of the lesion. In general, a biopsy showing adenocarcinoma indicates that the tumor is of rectal origin. Undoubtedly instances will occur where, after the most careful study, it will be impossible to grossly determine the exact anatomical site of origin. A case in point was a patient who was operated upon for anal fissure. The excised tissue was sent for pathological examination because it looked suspicious. It proved to be adenocarcinoma. Careful proctoscopic examination showed no gross evidence of tumor in the rectum. A course of intensive Roentgen therapy failed to completely eradicate the lesion. Radical excision five months later proved the lesion to be rectal in origin.

Errors in the correct determination of the precise anatomical site of origin are often due to the coexistence of fissure in ano, fistulae, prolapsed infected hemorrhoids or ischio-rectal abscesses. The presence of complicating lesions makes satisfactory examination difficult. Examination under anaesthesia may clarify the situation.

The importance of determining the exact site of origin of a tumor is becoming more evident as our experience grows in the study of response of various neoplasms, both to surgical and to radiation therapy. It is now fairly well established that tumors, even of similar histological configuration and from the same organ, may vary in their response to radiation therapy and, naturally, in their curability. This variation may be due to a characteristic inherent biological quality of tissue of origin, to the nature of the tumor bed, or to variations in accessibility of the neoplasm to the source of radiation. This difference in response to radiation therapy may be due to one or to a combination of the above factors. For example, squamous cell carcinoma of the aryepiglottic fold of the larynx is much more radio-resistant than a similar tumor arising from the epiglottis or ventricle, yet the accessibility to irradiation and histological patterns of both may be alike.

In general, adenocarcinoma of bowel origin has been found to be extremely radio-resistant unless doses approaching the destructive action of a cautery are used. Even amounts of radiation of such magnitude often fail to eradicate adenocarcinoma. Squamous cell carcinoma has been found to be more radio-sensitive. It is, therefore, logical to consider the use of radiation methods for anal cancers (which are for the most part squamous cell), thus, avoiding mutilating procedures which must be employed where the sphincter is involved. Anal tumors are accessible for precise intensive radiotherapy. If glandular spread has not occurred, a high rate of cure should be expected from radiotherapy.

The greater radio-resistance of adenocarcinoma and its relative inaccessibility to precise radiation methods when present in the rectum make

extirpative surgery the method of choice in operable cases. This point of view is held by many outstanding students of this question, (Regaud, Lockhart-Mummery, Sir Charles Gordon-Watson (4)).

Five cases[1] of squamous cell carcinoma of the anus are presented. Four were treated entirely by external irradiation (Roentgen therapy); one was treated by x-rays and interstitial radon.

CASE REPORTS

Case 1. History. H. B., a white female, age 70, was admitted on November 13, 1936. A mass which had been increasing in size for a period of 11 months was palpated near the anus. Bleeding was noted for a period of 3 months. An operation for rectal fistula had been performed thirty years previously.

Local findings. There was a sessile movable, ulcerated tumor, 3 x 4 cm. in size (Fig. 1). A biopsy was reported as "Squamous cell cancer."

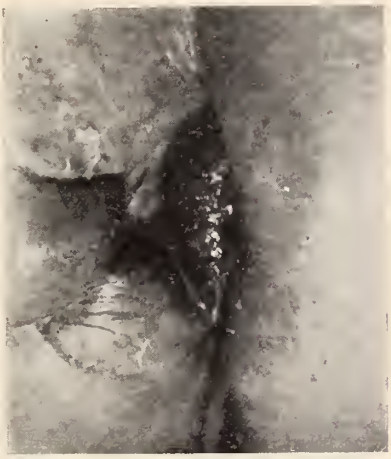

FIG. 1. Case 1. Before treatment

Treatment. From November 19 to December 12, 1936, with K.V. 180, filter 0.5 mm. Cu, 1 mm. Al, F.S.D. 50 cm., and size of field 6 x 8 cm., the following dosage was given: Anus direct 3500 "r" in air; right perianal 900 "r"; left perianal 800 "r".

Follow-up. There was no gross evidence of disease on June 20, 1940 (Fig. 2).

Case 2.[2] *History.* L. H., a white female, age 65, was admitted on January 23, 1936. A lump was noted near the anus for a period of 2 months. She experienced no pain.

Past History. She was treated at The Mount Sinai Hospital by radiation in 1933 for an anaplastic squamous cell carcinoma of the vault of the vagina, which had perforated the rectum. There had been no recurrence to date, August 13, 1940.

Local Findings. Two-thirds of the external sphincter of the anus was surrounded by an exophytic growth which was hard, fissured, ulcerated, and extended into the right lateral wall of the anal canal. The biopsy specimen was reported as, "Hornifying squamous cell cancer". (This case was considered a double primary neoplasm.)

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[1] One case from Tumor Clinic of Morrisania Hospital, Bronx, N. Y.

[2] Reported by Wimpfheimer and Harris (5).

Treatment. Roentgen therapy was administered from January 27, to March 23, 1936 with the following specifications: K.V. 180, filter 0.5 mm. Cu, 1.0 mm. Al; F.S.D. 50 cm.; size of fields 10 x 10 cm.; four fields cross-firing anus—2000 "r" to each (fractionated); total 8000 "r", measured in air.

Follow-up. On August, 1940, there was no gross evidence of disease.

Case 3. History. H. L., a white male, age 68, was admitted on July 7, 1938 (private case). He had experienced rectal tenesmus and bleeding, of 3 months' duration. An ulcerating tumor, 2 x 3 cm. was discovered arising from the right border of the external anal sphincter. A biopsy specimen was reported as "squamous cell cancer."

Treatment. He was treated from July 7, 1938 to August 17, 1938 as follows: K.V. 200; filter 1.0 mm. Cu, 3 mm. Al; F.S.D. 50 cm.; size of field, 5 cm. circle; one portal, anus direct; (fractionated) total dose, 4470 "r", measured in air.

Follow-up. In September, 1940 there was no gross evidence of disease.

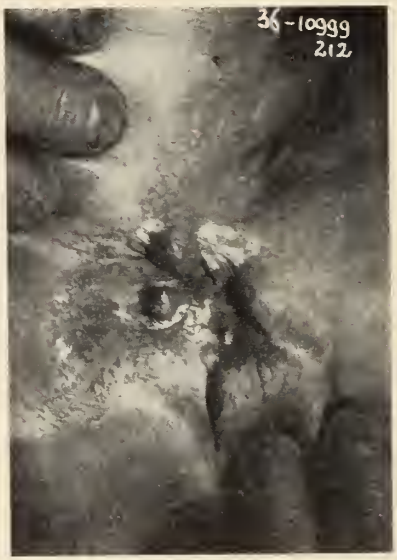

FIG. 2. Case 1. After x-ray treatment

Case 4. History. G. B., a white male, age 32, was admitted to the Morrisania Hospital on June 18, 1937. A lump was noted in the anus of 5 months' duration. He had experienced pruritis and occasional bleeding.

Past History. An abscess in the right groin had been drained three years previously and a diagnosis of lymphogranuloma had been made. There was a positive Frei test and the blood Wassermann was 4 plus (untreated).

Local findings. At the right border of the anal opening, an ulceration 2.0 x 1.0 cm. was seen. Infiltration extended around the walls of the anal canal and toward the rectum for a distance of 5 cm. No enlarged inguinal nodes were palpated. Biopsy specimen showed squamous carcinoma.

Treatment. Roentgen therapy from June 18, 1937 to August 6, 1937 was given as follows: K.V. 180; Thoraeus filter (2 mm. Cu equivalent); F.S.D. 40 cm.; size of field 6 x 8 cm.; one direct field with daily divided doses, totaling 4500 "r" in air.

Course. A marked diminution in the size of the tumor occurred, with ulceration of the residual nodule. Biopsy was negative. On February 6, 1939, 5 gold radon seeds, 0.7 millicuries each, were implanted, (filter 0.3 mm. Au; total dosage 465 millicurie hours). This did not control the growth of the nodule and slight tenesmus and itching persisted. On April 2, 1939 the anal mass was still enlarging; there were enlarged inguinal nodes; a large mass developed in the left lower quadrant, and proved to be a pelvic abscess which was drained successfully. The local condition of the patient failed to improve and he died at another institution on February 22, 1940 with active disease in the anal region.

Comment. Failure to cure in this case may have been due to under-dosage of the original treatment. A lesion of this type, extending into the rectal ampulla, might have responded better if radium had been used originally either in the form of implants or in a tandem surface applicator. The presence of lymphogranulomatosis and lues may have also modified the response to radiation therapy.

Case 5. History. J. L., age 52, a white male, was admitted to The Mount Sinai Hospital on March 8, 1940. He had experienced pruritis, bleeding and pain in the perianal region.

Local findings: An ulcerated neoplasm was disclosed, beginning within the anal canal, and extending anteriorly from the external anal sphincter along the perineal skin. The lesion was diamond-shaped, 6 cm. long, and 3 cm. wide. The biopsy report was, "Squamous cell cancer". Enlarged inguinal nodes were demonstrated.

Treatment. From March 11, to April 5, 1940 Roentgen therapy was administered as follows: K.V. 125, filter 1/4 mm. Cu, 1 mm. Al; F.S.D. 30 cm.; one direct anal portal, 8 x 5 cm.; 300 "r" in air, daily; total dose, 6600 "r".

Follow-up. In September, 1940, the ulceration was healed, but pruritis persisted. The irradiated area was superficially fissured; the inguinal nodes were unchanged. The final result is a healed lesion, although the pruritis still persists. This case is too recent for final evaluation.

Comment. Of the five cases treated by radiation therapy, the result in three cases has been satisfactory. One case is well for almost five years, one for four years and one for over three years. Case 4 was a failure, possibly due to under-treatment. Case 5 is too recent to evaluate.

DISCUSSION

No case showed definite glandular involvement except Case 4. In this patient, inguinal glandular deposits occurred in the terminal stage of the disease and treatment was, therefore, contraindicated.

Should definite inguinal node involvement occur, we would advise block dissection and possibly additional radiotherapy only if the primary anal lesion is healed and under control. Intraabdominal and pelvic glandular deposits spread via the superior and middle hemorrhoidal pedicles are beyond therapeutic aid.

It would seem from the experience with the above reported cases that external irradiation (Roentgen) through one portal of entry should be the treatment of choice. Occasionally, where extensive involvement of the canal is present, radium in tubes or implants may be added.

SUMMARY

1. Anal cancer is rare.
2. The majority of the cases are squamous cell carcinoma.
3. Biopsies showing adenocarcinoma are usually of rectal origin.
4. External radiation therapy (Roentgen) has given a satisfactory result in three out of five treated cases.

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CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

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The subject of congenital hypertrophic pyloric stenosis first became of general clinical interest at the beginning of the century.

Since then an attempt has been made to divide the condition into two distinct entities, pyloric stenosis, in which the presence of an hypertrophied pyloric muscle forms a tumor, and pylorospasm, in which no tumor is felt. Since at this time there is neither sufficient pathological nor clinical evidence to support this distinction, the condition should be looked upon as the dual manifestation of a single etiological factor. In reality pylorospasm and pyloric stenosis are not two separate conditions but merely different degrees of the same condition, namely, an involvement of the pyloroduodenal function occasioned by a disturbance of that portion of the autonomic nervous system which controls the gastro-intestinal tract.

The question of viewpoint is not merely of academic interest but is of profound importance in its effect upon therapy. If the problem is considered from the standpoint of two separate syndromes then medical treatment is proper for one and surgical treatment proper for the other. However, if the two are considered as different degrees of disturbed physiology then medical treatment is the logical treatment for all, with surgery reserved for those cases in which medical treatment fails.

Historically, the confusion resulting from the view that congenital hypertrophic pyloric stenosis and pylorospasm are different entities has been reflected in the fluctuating modes of treatment. At first medical treatment was used almost exclusively with fair success; however, a certain proportion of cases failed to respond to this mode of treatment and surgery was resorted to. Such procedures (1) as dilatation of the pylorus through an opening in the stomach wall, gastro-enterostomy, pylorectomy, and various forms of pyloroplasty were used with disastrous results, so that pediatricians hesitated to submit cases to the surgeon. Then medical treatment was generally followed until Rammstedt (2) in 1912, following the technic of Weber (3) of Dresden based on the suggestions of Fredet (4) of France, reported two cases with cures. In the first case the circular fibers were incised, the wound sutured transversely and covered with fascia. Although this child recovered, there ensued vomiting and other disturbances. In the second case the pylorus was merely incised, with results so satisfactory that he stated: "In the future I intend only to incise

the circular fibers being convinced that slitting of the muscular ring answers the purpose fully, by correcting the spasmodic contraction of the pylorus. The hypertrophy in itself will not cause disturbance if the spasm is corrected; this is rendered certain by the finding of an hypertrophied pylorus in children who have recovered from early stenosis and died of an intercurrent disease".

With the introduction of the Rammstedt operation, the results were greatly improved. In this country in the hands of certain surgeons notably, Downes (6), who introduced it to American surgery, the mortality was gradually reduced to a point where surgery offered an attractive method of treatment (7). As a result, although two excellent procedures, i.e. atropine (66, 67) and thick gruel (61) feeding had been introduced for its medical control, there was less and less resort to non-surgical methods until at present the tendency in this country is to submit to surgery all cases which do not immediately respond to medical procedures, usually inadequately applied.

The confusion resulting from the viewpoint of duality has also led to many diverse theories regarding the etiology of this condition. Some of the theories (7, 16, 17, 27, 28) advanced are:

(a) *The anatomical*, according to which the basis of obstruction is considered to be abnormal anatomy. To support this is offered x-ray evidence which shows the pylorus as a long thin line 4 to 5 times as long as normal which takes off abruptly from the dilated antral portion of the stomach. This view holds that the pyloric sphincter hypertrophies because of the relative obstruction caused by the elongated canal resulting in the development of a tumor (10). During the first three weeks the lumen is large enough to allow the passage of relatively small amounts of food but when larger amounts are required the passage becomes inadequate. Dietrich (29) believes that anomalous attachments of the pylorus are precursors of congenital hypertrophic pyloric stenosis.

(b) *The constitutional* theory stresses the importance of the familial evidence of the disease. Halbertsman (30) describes pyloric stenosis as a familial and hereditary condition and maintains that it should be regarded as a congenital malformation. Among his (10) thirty two cases it occurred several times in three families. Two of the families were related (31). Fabricius et al. (32) reported four cases in siblings the eldest of whom was a half sister to the other three. Pyloric stenosis has frequently been reported in binovular twins (33, 34). Svejcar (35) is inclined to believe that a constitutional factor exists since he considers the disease to occur so frequently among Anglo Saxon and Teutonic races and so rarely among Slavic and Latin peoples.

(c) *The allergic* theory is held by those (16, 43, 44) who believe in food sensitivity which has been shown to cause symptoms that may simulate pyloric stenosis.

(d) *The neurogenic* theory considers that pylorospasm is often only one manifestation of a general spastic state due to autonomic imbalance (13, 14). Hypertonia is always present and the condition, whether hypertrophic or not, is entirely due to spasm (15). Pharyngo-laryngo-entero-anal, and pylorospasm have been found in the same case (16, 17). The symptoms may be produced by reflex irritation as from an inguinal hernia (18), or as one English author believes from preputial phimosis. Emotional pylorospasm in a young woman is reported (19). Many cases show signs of neuropathy and fail to acquire a normal gastroduodenal reflex (20, 21, 22). This results in pyloric incoordination which causes a rapid development of muscular tissue, the whole stomach being involved, but chiefly at the pylorus. Failure to empty the stomach is not always due to obstruction but may be due to failure to relax (achalasia) (23).

Finally, in support of the thesis that the etiology points to a neurogenic origin are the beneficial effects of atropine, belladonna, and other drugs of this group which act upon the vagus nerve, of phenobarbital and opiates which have a special action on the gastro-intestinal tract through sedation, and of calcium through its well known action in lowering nerve irritability and its antispasmodic effect on smooth muscles (25).

In rats the condition has been produced by restricting vitamin B_1 in the mother's diet (26). In these animals the vagus nerves show myelin degeneration.

There is a vast amount of physiologic data supporting the neurogenic theory only a very small part of which is referred to below.

Gastric and intestinal tonus is a balance between acetylcholine, sympathin and the esterases (36). The gastro-intestinal tonus is greatly enhanced by mecholyl, especially if the bowel and stomach are tonic. This effect is markedly increased by previously or simultaneously administered doses of prostigmin. If sufficient prostigmin is used, a very small dose of mecholyl will produce profound results. This effect is *abolished by atropine.* The gastro-intestinal tonus is diminished by benzedrine, epinephrine and ephedrine—adrenergic drugs.

The older theory of the activity of bodily functions postulates that these are under the control of the autonomic nervous system and that a balance exists between the activities of the sympathetic and the parasympathetic division so that visceral functions are a sort of resultant of the balance of these two forces. The chemical concept of balance may be stated as the resultant of the effects of cholinergic and adrenergic substances plus the concept of the esterases.

Atropine sulphate has been used as the drug which inhibits the action of the parasympathetic nervous system, or more chemically, stops or prevents the action of acetylcholine or mecholyl. This action probably does not take place by paralyzing the parasympathetic system as has been supposed, but, as Loewi has shown, takes place at or near the reacting

cell. Whenever a balance obtains between cholinergic and adrenergic substances, atropine, by removing the cholinergic factor acts as a synergist to the adrenergic factor. Atropine relieves spasm of the stomach produced by section of the splanchnic nerves (37), and checks antral spasm produced by distention or irritation of the proximal colon (38). Reflex vomiting can be induced by distending an isolated pyloric pouch until the pressure within the pouch rises above a certain constant level which can be definitely measured (39). The afferent side of this reflex arc is entirely through the *vagus nerves.* Atropine increases both initial and final emptying times of the normal human stomach (40), which may be interpreted as a demonstration of the importance of the vagus nerve in maintaining the gastric tonus and peristalsis necessary for the normal emptying of the human stomach. Acids, alkalies, hypotonic and hypertonic solutions and solutions of organic acids have little or no influence on the pyloric sphincter when allowed to flow into the antrum (41). The height of antral contraction and outflow vary only with amount of inflow. "It is possible by pharmacologic experiment to reproduce many of the so called symptom complexes; i.e. achylia gastrica is simulated by the action of mecholyl; heart block can be readily produced by prostigmin and mecholyl; the spastic conditions of the colon, as well as the atonic one, can be reproduced by the use of mecholyl and benzedrine respectively. The *gradually developing theory that repeated functional disturbances may eventuate into organic disease has at last a working basis* in the effect of these drugs" (36).

It is suggested that symptoms of vagotonia may be due to suprarenal impairment as involution of the cortex of the suprarenals occurs during the first two weeks of life (42).

PATHOLOGY

Herbst (45) in a discussion of the histologic appearance of the intramural gastric nerves in pylorospasm stated that the intramural nervous system is the seat of the main changes, muscles and blood vessels being normal. There was degeneration of the cells and the axis cylinders of Auerbach's plexus. In some regions the ganglion cells as well as the nerves had round cell infiltrations, in other places nerve tissue structures were increased. The vagus nerves show myelin degeneration when hypertrophic pylorospasm is produced experimentally in rats (24). The circular muscle fibers become hypertrophied, the longitudinal fibers only slightly so.

SYMPTOMS

The symptoms of congenital hypertrophic pyloric stenosis are too well known to require extended comment. Onset at birth is rare. However it may begin either within the first few days of life or not until several months have gone by.

The fact that the symptoms are so rarely present at birth would seem to indicate that a tumor if present at that time must either increase in size or have some factor or factors added to cause obstruction to gastric emptying. It has been found that a tumor may be present early, late or not at all.

A tumor has been found several weeks after an inspection of the pylorus at which time no tumor existed (9, 10).

The reverse is also true. A tumor found at operation has later been absent (11, 12). As a matter of fact there may be complete obstruction without a tumor, and there may be a tumor without obstruction.

Males constitute over 80 per cent of the cases and the disease is frequent among first born. The diet seems not to be a factor as it occurs in breast as well as artificially fed infants.

Hypertonia, if looked for, will be found in all cases. There are usually projectile vomiting, small or absent stools, diminished urine or anuria, absence of sweating, visible gastric and sometimes intestinal peristalsis, loss of weight, and in many cases a pyloric tumor. X-ray examination reveals either delayed emptying time or complete retention. Occasionally there is spasm of other regions, pharynx, cardia, anus etc. The vomitus frequently contains blood and occasionally this is present in the feces (46, 47). Free hydrochloric acid is either absent or diminished (48). Total acidity is not greatly decreased (46). Hypochloremia parallels the symptoms together with a reduction in gastric and urinary chlorides (49, 50, 51).

DIAGNOSIS

The diagnosis depends upon the clinical symptoms of projectile vomiting, visible gastric peristalsis, diminished or absent urine and feces, loss of weight and often tumor. It must be differentiated from other obstructive lesions of the gastro-intestinal tract, such as duodenal atresia and obstruction by duodenal bands or adhesions (26, 52). The differentiation from congenital hypertrophic pyloric stenosis is usually made by the onset at birth, vomiting of bile, and x-ray evidence.

PROGNOSIS

The prognosis has been immensely improved since the early days. In reviewing the literature one is impressed by the fact that great improvement followed the introduction of procedures such as blood transfusions and the administration of parenteral fluids, all of which intended to overcome the metabolic disturbances caused by the vomiting. These patients grow up to be entirely normal individuals without gastrointestinal symptoms, although the literature contains references to the contrary. They do seem, however, to be more prone to vomit than the average individual.

TREATMENT

The literature of the past ten years shows that opinion regarding the treatment of congenital hypertrophic pyloric stenosis is almost equally divided between those favoring surgical and those favoring medical procedures. Both views are fortified by equally strong statistics. Some have abandoned surgical for medical treatment, and vice versa, demonstrating that the condition is one which apparently can be treated successfully by either method. All cases should first be treated medically. The argument formerly advanced, that delay in referring cases to the surgeon accounted for most of the failures of surgery, is refuted by some of the highest authorities in the surgical treatment of this disease. Donovan (53) nullified this argument in the following words: "I now feel there is no need to hurry operation even though a child is vomiting everything. One or two preoperative transfusions are used, 20 cc. of whole blood per kilo of body weight. Alkalosis is usually present with high concentration of serum carbon dioxide; therefore, all receive clyses of 100 cc. of sodium chloride solution (1 to 4 in number). It is amazing how one can convert a bad surgical risk into a fair one in two or three days". In substantiation of this statement he reports 243 cases operated upon with only one death. Lanman and Mahoney (54) state: "the operation is not an emergency. Owing to the glycogen depletion from starvation 10 per cent glucose is used to overcome the ketosis, in addition to blood transfusion, etc." They report 150 cases with a mortality of 2 per cent.

Treatment by either surgical or medical methods must always take into account the patient's chemical status. Thus, the loss of chlorides due to the vomiting regularly produces some degree of alkalosis which requires treatment. The anhydremia due to the loss of body fluids must be corrected, while the low serum protein from starvation is raised and the general condition is greatly improved by transfusion of blood.

The Rammstedt operation or some slight modification of it has been universally accepted as the ideal surgical procedure. The operation consists of a simple incision of the circular muscle fibers of the pylorus down to the mucosa. When one contemplates the results of Donovan, Downes' successor at the Babies Hospital, and such men as, Lanman, Mahoney, Straus (8) and other surgeons of large experience, one is inclined to feel that surgery is the treatment of choice. However, there is another side to the picture. Such results are only obtained by surgeons experienced in the operation in collaboration with an excellent pediatric staff of physicians and nurses working in the best environment. The number of men who have obtained similar results is small.

Even today, outside of a group of surgeons of large experience, surgically treated cases have as high a mortality as those treated medically. It has been urged that only two weeks hospitalization is required for a surgical

cure. Under medical treatment however hospitalization is only occasionally required and the home treatment is simple.

There is no unanimity of opinion regarding the non-surgical treatment of congenital hypertrophic pyloric stenosis. The recommendations are many and varied, all having for their object the relaxation of these same muscle fibers. *Atropine sulphate* in my hands and in those of many others has proven a safe and efficient drug. In recent years (55, 56) atropine methylnitrate (Eumydrine) 0.25–0.40 mg., in solution, twenty minutes before feeding has been highly lauded, apparently with full justification judging by results. Any drug of the atropine group may be used. Phenobarbital has gained wide approval and is most valuable in this condition. Calcium should be used in every case (57, 58, 59, 60).

Dietary measures are infinite in variety. The food should be concentrated in form. A plain milk formula is least desirable. Sweetened condensed milk has been recommended upon the basis of a possible milk allergy. Best and most favorably known is the thick gruel feeding, an effective measure which has stood the test of time. Gastric lavage and hypodermoclyses or intravenous drip of normal saline solution are valuable adjuvants. X-ray treatment of the upper part of the chest over the manubrium is advocated for its effect upon the vagus nerves (62). Dilating the pylorus with a duodenal catheter has occasionally succeeded in relieving the symptoms (14). Diathermy relaxes pylorospasm in dogs and its use has been suggested for congenital hypertrophic pyloric stenosis of infants, in whom it has been tried with varying success (63).

These recommended procedures are all of value, but the fundamental requirement in the treatment of this condition is the relaxation of the pyloric sphincter. Atropine, in one of its forms, plus calcium best fulfill this requirement. All other recommended procedures are but valuable adjuvants, some of them of outstanding importance such as phenobarbital and thick gruel. The atropine treatment of congenital hypertrophic pyloric stenosis is eminently satisfactory when properly carried out.

There have been several fundamental difficulties in popularizing this treatment, the first and the most important being the quality of the atropine used. It has been shown that in solution it deteriorates rapidly, and in usual tablet form it is unreliable in dosage (64). The deterioration is readily obviated by only using an atropine solution freshly made in the home. Accurate dosage is achieved by using the homeopathic tablet, gr. 1:1000, which is correct in its dosage and reliable in its action and can be procured at any Homeopathic Pharmacy; or by using hypodermic tablets of any reliable drug house from which a solution of 1:1000 can be made, to be used the day it is prepared, and prepared fresh daily.

The second difficulty is inadequate dosage. For some reason difficult to explain, atropine has the reputation of being a dangerous drug. This is entirely contrary to my experience which covers a period of over twenty-

five years and its use in thousands of cases including pylorospasm, hypertonia, vomiting from any cause, enuresis, asthma, enterospasm, etc. Two of the reasons for this fear is the inaccuracy in strength referred to above and the readiness with which the signs of physiologic effect appear. I have used doses as high as gr. $\frac{1}{6}$ in twenty-four hours in a three weeks old infant. I have seen a temperature as high as 109°F. in a case not properly supervised, and frequently temperatures of 106°F. and 107°F. There have occurred delirium, restlessness, obstipation, flushing, dryness, dilatation of pupils, even projectile vomiting due to the atropine given, but never have I seen a lethal outcome nor later ill effects, and in none was it necessary to do more than withdraw the drug for a few hours until the symptoms had subsided after which the drug was resumed. The feeling that atropine is dangerous results in a discontinuance of the drug with the first appearance of signs of its physiological action, such as redness of the face, dryness of the throat, dilatation of pupils, fever or restlessness. If the next few doses are omitted until these signs have disappeared and then replaced by a smaller one, it is often found that the dose which at first produced symptoms can soon be exceeded. The dosage of atropine to be used in a given case varies. It may be impossible in the beginning to use more than gr. 1:2000 at each feeding, or it may be found that maximum doses are required before the desired result is obtained.

In pyloric stenosis gr. $\frac{1}{20}$ or gr. $\frac{1}{16}$ in twenty-four hours is usually necessary to obtain relief from symptoms. Although the dose may differ greatly for different patients, it is fairly constant for the same patient at different times. This also holds true for other drugs affecting the autonomic nervous system (36).

The procedure which I have followed is to use breast milk if available. Next in choice is protein milk, then evaporated milk. With artificial feeding some sugar or thick gruel feeding is added in amount suitable to the size of the infant. The feedings are given not oftener than every four hours; six hour intervals are sometimes better. In each feeding there is placed atropine sulphate gr. 1:1000. If vomiting continues after two feedings the dose of atropine is increased by the addition of another gr. 1:1000, and is increased in this way every second feeding until the vomiting is controlled or the signs of atropine intoxication require a temporary reduction in dosage. It is only rarely necessary to use the drug hypodermically. When the indication exists, clyses or saline drip with or without glucose, and occasionally a blood transfusion are used. Saline solution (750 to 1500 cc.) by continuous drip is said to be superior to single small injections, in combating dehydration, alkalosis, and disordered chloride metabolism (65).

Calcium gluconate, drams one is added to the day's formula. When the atropine dosage is raised to the point of tolerance and sufficient relief is not obtained $\frac{1}{4}$ gr. phenobarbital is added to each feeding. In some cases

the dose of phenobarbital must be increased. The infant should be handled as little as possible and kept in a semi-upright position turned toward the right side. Under this treatment the vomiting may be controlled at once or perhaps only after a week or two. The medication will have to be continued over a variable period, in some cases extending to months. After the acute phase the medication becomes part of the feeding routine. From time to time an attempt is made to reduce the dose of atropine, and if there is no recurrence of vomiting it is discontinued. These cases do not relapse, they feed normally and develop well. There may be occasional projectile vomiting during the course of treatment.

Hospitalization is rarely required except in those cases in which the absence of intelligent cooperation or economic circumstances create conditions making hospitalization imperative. Early resort to surgery is desirable here because these children can be returned to the home as normal feeding cases in a shorter time than when treated otherwise; but unless an experienced operator with a trained staff is available even these cases should be given medical treatment.

The tendency to submit cases of pyloric stenosis to surgery without adequate medical treatment, in view of the good results obtained by the latter when properly applied, is not in keeping with good medical tradition. The brilliant results of surgery in good hands is not a valid reason for submitting an infant to operation. However, there are several very good reasons for surgical intervention: if an experienced surgeon is available, the absence of ability in the home to properly cooperate in the treatment, and the failure of proper medical treatment.

In one case which had improved on atropine, there was a sudden failure. It was found that atropine fixation had occurred and although several different brands of hypodermic tablets were used in unheard-of doses, no dose of the drug had the slightest atropine effect. Operation cured this case.

A review of the literature of the last ten years shows that the mortality with surgical treatment (2840 cases) was 6 per cent and with medical treatment (1218 cases) 7.8 per cent.

In my own series, totaling 179 cases, 8 were operated upon after failure of medical treatment with 7 recoveries and 1 death. Of 171 medically treated cases there were but 2 deaths, both occurring in the recovery phase when the atropine dosage had been reduced. The cause of death was not explained clinically and autopsies were not permitted.

SUMMARY

1. Pylorospasm and pyloric stenosis are only different degrees of the same condition produced by a disturbance of the autonomic nervous system. Despite the fact that most cases can be cured by medical methods there has been an unjustified tendency to resort to surgery.

2. The results of surgery where excellent are obtained by a limited number of experienced surgeons in collaboration with the medical and nursing staffs of pediatric hospitals. The results of surgery outside such a group are not as good as those obtained by non-surgical measures.

3. The great reduction in mortality, whether under medical or surgical treatment, followed the introduction of such procedures as blood transfusion and the parenteral administration of fluids.

4. The surgical treatment of choice is the Rammstedt operation.

5. The medical treatment includes atropine sulphate, calcium, phenobarbital, thick gruel feedings, parenteral fluids, etc.

6. A review of the literature of the past ten years shows 2840 cases treated surgically with a mortality of 6 per cent and 1218 cases treated medically with a mortality of 7.8 per cent.

7. Of 179 cases in the author's series, 8 were treated surgically with 1 death and 171 were treated medically with 2 deaths.

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THE USE OF AMINOPHYLLINE FOR POST-ANESTHETIC COMA

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Coma after operation is always a serious complication. Yet it is only quite recently that attention has been focused on cerebral damage from anesthesia as a possible cause of post-operative mortality. Before the anesthetic itself can be denounced as the cause of post-surgical coma, the more common renal, metabolic and pulmonary complications must be excluded. I wish to present herein a case of post-anesthetic coma, in which the intravenous administration of Aminophylline was found to have been an effective therapeutic measure after all conventional means had failed to ameliorate the condition.

CASE REPORT

History. Mrs. G. G., age 68, white, entered the Good Samaritan Hospital on December 4, 1937 after a diagnosis of carcinoma of the stomach had been made. Laboratory findings at the time of admission were: hemoglobin, 30 per cent with 2,250,000 red blood cells; urine, negative with a specific gravity of 1022. X-ray examination of the stomach showed a complete pyloric obstruction with an enormous dilatation of the stomach. Continuous gastric drainage was instituted, and the patient's nutrition was maintained by intravenous glucose infusions. Two transfusions, each of 500 cc. of whole blood, were given. Ten days later (December 14, 1937) the patient's condition had improved sufficiently to warrant operation. Her temperature was 98.2°F.; pulse rate, 80 per minute; blood pressure, 104 systolic and 44 diastolic.

At operation a freely movable carcinoma of the pylorus, without any involvement of the regional glands, was found. A typical Polya gastric resection was undertaken.

Preoperative medication consisted of Pentobarbital 3 gr. and atropine $\frac{1}{150}$ gr. The anesthetic was begun at 10:30 A.M. Nitrous oxide and oxygen were used for induction and maintained for a period of twenty minutes. Shortly after the start of operation the anesthetist reported that the patient had suddenly stopped breathing. Her blood pressure was falling rapidly. However, before resuscitative measures could be employed, there was a resumption of breathing and her condition became satisfactory. The nitrous oxide was discontinued after this episode of apnea. Cyclopropane with oxygen was used for the remainder of the operation.

The surgery was completed at 12:40 P.M. Except for the one apneic episode, the blood pressure fluctuated during operation between 120 to 90 systolic and 70 to 60 diastolic. Immediately after the surgery the patient was again transfused with 500 cc. of whole blood, and her condition appeared satisfactory. At 2:00 P.M., on the day of operation, the nurses' notes were as follows: "Patient moaning, restless and does not respond." The pulse rate varied from 98 to 140 per minute throughout the remainder of the day. On the following morning the patient had not yet responded.

A laboratory test to determine the possible cause of coma indicated no renal impairment. The blood urea-nitrogen was 37 mg. per 100 cc.; the carbon-dioxide com-

bining power was fifty volumes per cent. This ruled out an acidosis. The report of 530 mg. per 100 cc. of sodium chloride showed no chloride deficiency. There was a negligible temperature for forty-eight hours after operation, but this was never high enough to account for the coma. Except for a few moist râles at both bases of the lungs, presumably hypostatic in origin, there were no significant pulmonary findings. A painstaking neurological examination to determine the cause of the coma was negative. The blood pressure remained at 120 systolic, which, with the lack of other evidence of arteriosclerosis, precluded a possibility of a cerebro-vascular accident. The results of an examination by stomach tube, as well as the absence of tympanites, excluded the possibility of a postoperative gastric dilatation or peritonitis. The constancy of the pulse rate and blood pressure made a diagnosis of internal hemorrhage untenable. The eventual diagnosis of post-anesthetic coma was arrived at by exclusion.

Caffeine and Coramine alternated every two hours produced no change in the coma. As a supportive measure, carbon-dioxide was administered every hour to prevent a pulmonary complication. The general condition was maintained by venoclysis. Pitressin was administered at four hour intervals as a prophylaxis against postoperative distention or ileus. Each dose of Pitressin was followed by involuntary bowel movements and urination. Two transfusions of 500 cc. each of whole blood were given on the second and fourth postoperative day. Still the coma was uninfluenced.

This condition persisted until December 19, 1937, a period of five days following the administration of the anesthetic. At 10:30 P.M. on that day, 20 mg. of Benzedrine sulphate were used intravenously with no perceptible response. Then, a half hour later, 0.24 gram of Aminophylline was injected intravenously. During the administration of this drug, the patient slowly began to move, and then to mumble incoherently. Shortly after the injection was completed I put water into the patient's mouth and was able to elicit a slow response to my command, "Stick out your tongue and swallow." Following this amazing result, 0.48 gram of Aminophylline was given intravenously every four hours. The patient became progressively more restless and gradually more consciously responsive. Forty-eight hours after the institution of therapy, she responded rationally to conversation and volunteered the information that she was having abdominal pain. From this time on Aminophylline was discontinued, and the patient went on to an uneventful recovery. No neurological or cerebral sequelae manifested themselves after the disappearance of the coma.

At the time of this report, seven weeks after operation, the patient is completely symptom-free and reveals no sign of any cerebral damage.

COMMENT

Persistent coma following anesthesia is now thought by many pathologists to be due to cerebral anoxemia caused by asphyxia. The immediate nervous symptoms may assume the pattern of generalized convulsive seizures, muscular rigidity, or persistent coma. Frequently these cases terminate fatally, sometimes with signs of decerebrate rigidity. Delayed manifestations may appear in the form of psychosis, of a Parkinsonian symptom complex, disturbances of specific sensation or in various other neurological upsets. The patient may recover entirely from an anoxemic episode, may survive for a variable period with residual symptoms, or may die within a few days. In the fatal cases reported, death usually occurred

within two to seven days; occasionally after an interval of weeks or months. The clinical symptoms and pathological findings in these cases plainly disclose asphyxia. They are, *per se*, not due to any chemical change, but are produced by the damaging action of the gas itself. The mechanism seems to be one of two types, (a) sudden circulatory and/or respiratory failure, together with considerable cerebral impairment due to inadequate oxygen supply, or (b) prolonged exposure of the brain to partial asphyxia.

The damage wrought by the anoxemia depends on its degree and duration. Pathologically there may be (1) a sclerosis of scattered pyramidal cells, (2) discrete pale areas throughout the brain, (3) patchy necrosis of the central or deep cortical layers, (4) a subtotal destruction of the cortex or, if the patient survives for sufficient interval, (5) vascular scars due to formation of new blood vessels.

There is no certain predictability as to the cortical area that may be involved, hence the variable clinical picture. The literature describes *persistent* coma as the most serious cerebral manifestations of anesthetic damage. It is interesting to note that severe and even fatal trauma to the cerebral cortex may ensue from anesthetic anoxemia without cyanosis.

In a critical analysis of fifteen cases, eleven of which came to autopsy, Courville observes that in those which terminated fatally and had serious residual manifestations, a state of deep coma had been present, from which the patients could not be roused. Furthermore, he states that the persistence of coma for two or three days is generally an ominous prognostic sign.

The use of Aminophylline in this case was suggested by Dr. Morris Nathanson. He had observed, during the course of research work on the treatment of Cheyne-Stokes breathing with Aminophylline, that comatose patients frequently returned to consciousness after the administration of the drug.

Aminophylline is ethylene-diamine-theophyllin, a purine body related to caffeine. It has been used chiefly in the treatment of hypertensive cardiac conditions associated with pain, such as angina pectoris, coronary sclerosis and coronary thrombosis. It also has been used in cardiac dyspnea, asthma, and, in conjunction with digitalis, in the treatment of heart block and cardiac failure.

The administration of Aminophylline results in a vasodilation of the coronary and peripheral vessels and cardiac stimulation. As a vasodilator it has a more prolonged action than nitroglycerine. The only studies that point to its cerebral action are in connection with its use in Cheyne-Stokes breathing. Up to the present time there appears to have been no discussion in the literature of the cerebral action of Aminophylline. It is to be hoped that the report of this case will stimulate further studies on the use of Aminophylline in comatose states that are specifically cerebral in origin.

THE DIAGNOSIS OF BLADDER NEOPLASM IN BENIGN PROSTATIC HYPERTROPHY

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The concurrence of bladder neoplasm with benign prostatic hypertrophy is not rare. These conditions are usually readily determined by cystoscopic examination. There are some cases, however, where the prostatic enlargement is so marked that a concomitant neoplasm of the bladder is difficult to recognize or is entirely overlooked. The importance of such an error in diagnosis is self evident. This paper, therefore, has a two-fold purpose. Firstly, it presents four cases which illustrate clearly the problem involved. Secondly, it discusses the factors which lead to diagnostic error and the means of avoiding them.

CASE REPORTS

Case 1. History. (Adm. 319767.) M. H., a 52 year old man was first seen at the office May 6, 1930 because of gross hematuria. Examination showed nothing of note except for a considerably enlarged prostate by rectum and two ounces of residual urine. Cystoscopy under local anesthesia revealed a marked intravesical enlargement of the prostate and some hemorrhagic areas over the base of the bladder. The bleeding was thought to arise from these areas as well as from the enlarged prostate. He was again seen on November 21, 1934 because of repeated terminal hematuria. Due to a fairly recent coronary thrombosis and because the previous cystoscopy had shown a marked prostatic hypertrophy, it was felt that further cystoscopy should be deferred unless the urinary bleeding persisted. On March 25, 1936 he was admitted to the hospital for cystoscopy under anesthesia. Marked intravesical enlargement of the median and lateral lobes was again seen. In addition, an irregular neoplasm was visible on the posterior wall of the bladder. The entire growth could not be seen because it was obscured by the left lateral lobe of the prostate. The growth was lightly fulgurated and the biopsy was reported as "inflamed papilloma with squamous cell metaplasia." One week later he was again cystoscoped under gas and oxygen anesthesia. There was considerable bleeding from the prostate and the growth was thoroughly fulgurated. He left the hospital on April 3, 1936. He was readmitted to the hospital five days later with a profuse and massive hematuria filling the bladder with clots which could not be evacuated by conservative measures. This severe bleeding was thought to be prostatic in origin. Suprapubic cystostomy was done under spinal anesthesia. The bladder was distended with a large number of clots which were evacuated. A large papillary growth about 5 centimeters in diameter was found. This was situated behind the left ureteric orifice and partially covered by the large prostate. The growth was thoroughly fulgurated and specimens removed at this time were reported "papillary carcinoma." A second stage prostatectomy with the introduction of five $2\frac{1}{2}$ millicurie radon seeds into the base of the tumor was done on May 4, 1936. The patient made an uneventful recovery and has been well since then.

Summary. This patient with hematuria was first cystoscoped under local anesthesia and no tumor was found. The bleeding was attributed to his large prostate and to hemorrhages in the bladder. With recurrence of hematuria, cystoscopy under anesthesia showed a part of a tumor, the main growth being covered by the prostate. A subsequent suprapubic cystostomy for a profuse bladder hemorrhage revealed a large papillary carcinoma of the bladder.

Case 2. History. (Adm. 420666.) M. V., a 74 year old male was first seen June 30, 1937 with a history of intermittent hematuria four months in duration. He had a few ounces of bloody residual urine. A cystogram showed a large bladder with multiple diverticula and a large prostatic intrusion. The symptoms were thought to be prostatic in origin. On August 10, 1937 he was admitted to The Mount Sinai Hospital with profuse hematuria. This was controlled with an indwelling urethral catheter and bladder irrigations. Intravenous urography was done but failed to visualize the kidneys. He was discharged from the hospital on August 24, 1937 but had to be readmitted on September 16, 1937 because of a recurrence of the urinary bleeding. Four days later he was cystoscoped under anesthesia and an enormously enlarged prostate was seen. A transurethral resection was performed with the removal of 46 grams of tissue. On October 3, 1937 an additional 22 grams of prostatic tissue were removed transurethrally. He left the hospital on October 23, 1937, voiding well and with only a few ounces of residual urine.

The hematuria continued intermittently. He was readmitted to the hospital on November 11, 1937 and given a transfusion of 500 cubic centimeters of citrated blood. A few days later a cystoscopy under spinal anesthesia still showed some prostatic tissue. No neoplasm was seen in the bladder. Intravenous pyelography showed visualization of the right kidney but no excretion of opaque material from the left kidney. Four days later he was again cystoscoped under spinal anesthesia and this time a large irregular flat neoplasm in the region of the left ureteric orifice was seen. This area was fulgurated and specimens removed showed an infiltrating squamous cell carcinoma of the bladder.

He was given deep x-ray therapy but the hematuria and dysuria persisted. His last admission to the hospital was on February 15, 1938. He entered with profuse hematuria with the passage of clots. His hemoglobin was 30 per cent. A large mass was felt in the pelvis. His general condition deteriorated progressively and he died in coma on April 2, 1938.

Summary. This patient with intermittent hematuria and an enormously enlarged prostate had a cystogram and several cystoscopic examinations under anesthesia. It was not until after a large amount of prostatic tissue was resected transurethrally that an infiltrating neoplasm of the bladder was found.

Case 3. History. (Adm. 435591.) E. R. was a 73 year old male who was admitted to the hospital on November 29, 1938 with a history of increased difficulty and frequency of urination for a period of several years and with complete urinary retention for forty-eight hours. His prostate by rectal examination was considerably enlarged, soft and smooth. Intravenous urography revealed a moderate bilateral ureterohydronephrosis and the cystogram shadow showed a marked intravesical enlargement of the prostate. On December 2, 1938 a bilateral vasectomy and suprapubic cystostomy were performed. A large intravesically enlarged prostate was palpated within the bladder. His postoperative course was complicated by fever which was attributed to a silent pyelonephritis. He was discharged from the hospital on January 6, 1939 with the suprapubic tube draining well and with his general condition improving.

He was readmitted to the hospital on January 30, 1939. Intravenous urography

at this time showed a diminution in the degree of dilatation of the right upper urinary tract as compared with the previous x-rays. The left side, however, failed to visualize at this time. Since this patient was considered a poor surgical risk, it was felt that if a transurethral resection would be possible it was preferable to a second stage prostatectomy. Despite spinal anesthesia, it was impossible to introduce the cystoscope through the prostatic urethra. A second stage suprapubic prostatectomy was therefore done, enucleating two very large lateral lobes of the prostate. The biopsied specimen was reported to be a "fibroadenoma."

The postoperative course was complicated by a persistent suprapubic fistula and the onset of myocardial failure with dyspnea, orthopnea and dependent edema. He was discharged from the hospital on March 28, 1939 with an indwelling urethral catheter. His condition at home was characterized by a slow and progressive downhill course with symptoms of cardiac failure and repeated episodes of bleeding from

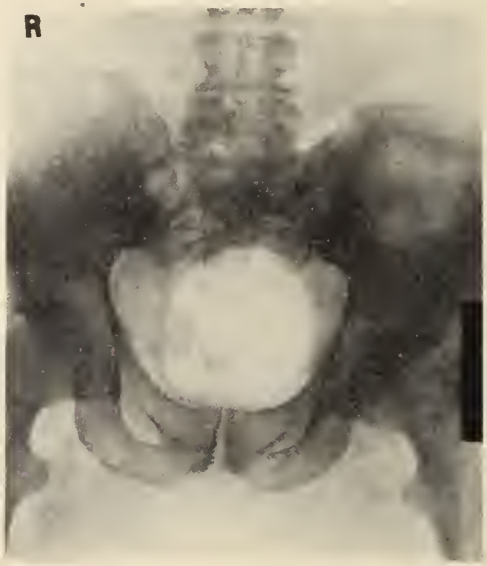

FIG. 1. Case 4. Aerogram of bladder showing filling defect on right side of bladder

the suprapubic sinus. At times the hemorrhages from his bladder were profuse and filled the bladder with clots. Several months later he developed a small nodule in the suprapubic scar which gradually increased in size. In March 1940 he began to fail rapidly, the metastatic deposits in his penis and suprapubic scar increased in size and he died a few weeks later.

Summary. This patient had a markedly enlarged prostate. No evidences of neoplasm were visible on the cystogram x-rays. An attempt to cystoscope him under anesthesia was unsuccessful. Following a suprapubic prostatectomy he developed a persistent suprapubic sinus with repeated episodes of hematuria, metastatic deposits in the suprapubic scar and penis and died with the clinical picture of carcinoma of the bladder.

Case 4. History. (Adm. 454638.) C. W., a 71 year old man was treated in the past with prostatic massages. In January 1940 he developed lumbar back pain which was relieved by adhesive strapping. He then noted intermittent hematuria

which on some occasions was initial and on others terminal. Because it was thought that this was due to his enlarged prostate, he was given six deep x-ray therapy treatments to the prostate. He was first seen by us at the office on March 5, 1940. His urine was smoky with only one ounce of residual urine on catheterization of the bladder. His prostate by rectal examination was considerably enlarged. Cystoscopy was performed under local anesthesia. There was very marked intraurethral and intravesical enlargement of the lateral lobes of the prostate. The urethra was so elongated that a good visualization of the bladder was unsatisfactory (Fig. 1).

He returned one week later for cystographic roentgen ray examination. The antero-posterior view showed a normal bladder outline with a marked intrusion of the prostate. In the left oblique view there was a notching on the right side of the bladder shadow which was also evident in the aerogram film. In view of this finding he was admitted to the hospital on April 2, 1940. Cystoscopy was performed under spinal anesthesia using the twelve inch cystoscope. A neoplasm on the right side of the bladder was found which had the appearance of a papillary carcinoma. The growth was thoroughly fulgurated. Control cystoscopic examination on June 7 and June 27, 1940 showed no evidence of any neoplasm in the bladder. The patient has had no further evidences of gross hematuria.

Summary. This patient who had repeated hematuria was cystoscoped under local anesthesia and a large prostate covered with dilated veins was found. Because of the unsatisfactory visualization of the bladder, cystography and cystoscopy under spinal anesthesia with a long cystoscope disclosed the presence of a bladder neoplasm which was effectively treated by fulguration.

DISCUSSION

Although hematuria is the cardinal symptom of neoplasms of the bladder, it is commonly associated with prostatic hypertrophy. Debenham (1) estimated that 10 per cent of the hematurias in men are due to benign prostatic enlargement. The degree of urinary bleeding in the latter condition may be so profuse as to necessitate emergency surgery to avoid a fatal issue from hemorrhage. This subject has been presented by us in a previous publication (2).

We are not concerned with the small or moderate-sized prostatic hypertrophies where an excellent cystoscopic view of the bladder can be obtained. Errors of diagnosis under such situations are due to carelessness. To clarify the type of case in which one is likely to err, it might be best to describe a composite picture. The patient is usually over 65 years of age and gives the characteristic history of prostatic symptoms over a period of months or years. He comes to the urologist not only because of an increase in the degree of urinary frequency, nocturia and dysuria but mainly because he noticed gross intermittent hematuria. His prostate is considerably enlarged by rectum and the amount of residual urine has the normal variation. Cystoscopy under local anesthesia is usually unsatisfactory for several reasons. The gland may be so vascular and may bleed so much on introducing the cystoscope that the field of vision is obscured. He may be intolerant to cystoscopy. The urethra may be so elongated that one can only visualize an enormously enlarged prostate. In some instances it may be impossible to introduce the instrument. At

any rate, a good inspection of the bladder is not obtained and the examiner may feel satisfied that the trouble results from the enormously enlarged and vascular prostate gland. This diagnosis seems so simple and obvious that the possibility of an associated bladder neoplasm is not even entertained. It is just this type of case in which a thorough investigation of the urinary tract is so essential. In any patient with hematuria which is thought to be prostatic in origin, other lesions in the bladder and upper tracts must be excluded before one can safely state that the prostate is the responsible source for the bleeding.

The first diagnostic procedure to be performed should be excretory urography. Vintici and La Roche (3) performed an urgent primary prostatectomy on a man for a profuse hemorrhage into the bladder which was filling it with clots and in whom the bleeding was subsequently proven to come from a renal neoplasm.

The next diagnostic step is cystography. The technic ordinarily employed for cystograms is so standardized that the full diagnostic value of the procedure is often lost where it is most necessary. The routine use of 5 or 6 per cent sodium iodide solution is not conducive to the best results. This medium is so strongly opaque to the Roentgen rays that it can readily obscure a small lesion in the bladder. We have been employing a concentration of hippuran solution varying from $3\frac{1}{2}$ to 8 per cent. The weaker strength is used in the very thin patient while the stronger solutions are introduced into the more obese individuals. The degree of opacity thus obtained is such that filling defects in the bladder shadow are more readily demonstrable. Both antero-posterior, oblique and aerogram exposures are made.

Last, but not least, is the repetition of cystoscopy. This should be done in a hospital and under spinal anesthesia. A dosage of 35 or 40 milligrams of procaine introduced between the 4th and 5th lumbar vertebrae will give a perfect anesthesia. With the resultant relaxation a cystoscope can be introduced with minimal trauma or bleeding. If the urethra is unusually long, we use the long, or 12 inch, Brown Buerger cystoscope. To complete the examination of the bladder neck and area behind the prostate we have employed the retrograde lens telescope.

It is only by such careful diagnostic procedures that one can avoid the pitfalls and fail to recognize a neoplasm of the urinary tract in the presence of marked prostatic hypertrophy. One should always be on guard when such a patient exhibits intermittent gross hematuria.

SUMMARY AND CONCLUSIONS

1. A neoplasm of the bladder can easily be overlooked in patients with marked prostatic hypertrophy.

2. The presence of intermittent hematuria calls for a complete investigation of the urinary tract.

3. Suggestions for more satisfactory cystographic examinations have been made.

4. Cystoscopy under spinal anesthesia in a hospital, with the use of the long cystoscope and of the retrograde lens telescope, should be utilized in the above type of cases.

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GASTRODUODENAL ULCER IN INDIVIDUALS MORE THAN FIFTY YEARS OF AGE

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While it is generally known that gastroduodenal ulceration can occur at any age, the majority of cases group themselves between the ages of twenty and fifty years. Acute ulcers also appear in the newly born and Kennedy (1) has noted hemorrhage and perforation in childhood. Hemorrhage and perforation have also been reported in patients of very advanced years who had given no previous history of ulcer. Crohn (2), quoting the combined statistics of C. F. Martin in Osler and McCrae's System of Medicine, indicates that 58.6 per cent of cases occur between the ages of twenty and fifty years. At the Mayo Clinic the average age of onset for duodenal ulcer was thirty-three years. In the main, the onset of symptoms in gastric ulcer is approximately ten years later than in duodenal ulcer, and this ratio holds true for both males and females. If the time interval between the onset of symptoms and the time when the patient first seeks medical or surgical treatment is considered it is more than likely that over a half of the cases present initial symptoms between the ages of ten and thirty years.

It is very fortunate that despite the large incidence of gastroduodenal ulceration the great majority of patients respond adequately to ambulant medical care. The symptoms in this group are mild, readily relieved by diet and antiacid medication. The exacerbations occur at prolonged intervals and are easily controlled. However, all cases do not respond so favorably. Without wishing to discuss the question of definitive healing in ulcer, either pro or con, it may be said that clinically it has been amply demonstrated that in certain patients the ulcer symptoms become recurrent over shorter time intervals, with complications of a life-threatening nature. In others, the course is unremitting. This group of refractory patients, with prolonged ulcer histories, frequently pass middle age unrelieved by medical management. More and more of these patients in the advanced age groups present themselves in the wards and the Out-Patient Department of the hospital with ulcers of the stomach and duodenum. Some require surgical intervention and because of their age, they are specifically interesting and trying problems. Others require fine judgment as to whether medical therapy should be continued. It should not be assumed that all of these cases represent medical failures. Years ago, it was observed that an increased incidence of ulcers in individuals past

middle age could be postulated on a vascular basis. This concept forms one of the many theories of ulcer formation particularly applicable to those patients who present themselves with a short history in later life. On the same basis, this group presents the more uncommon complications of ulcer, namely, hemorrhage and obstruction. For this reason it should prove of value to review those cases of gastroduodenal ulcer past middle life, which were admitted to the wards of The Mount Sinai Hospital over a five year period (1935 to 1940). The cases also include those patients whose symptoms commenced before the fiftieth year but whose subsequent readmissions for ulcer brought them within the age group under discussion. In some instances, the patients were admitted for conditions unrelated to the ulcer which was revealed either by roentgenograms, previous Out-Patient Department examinations or by necropsy. It should be noted that both gastric and duodenal ulcers were included as a group. Although certain clinical and biological differences are present in these conditions and since these differences are pointed out and alluded to in the discussion, it is inadvisable in a broad review to segregate such clinically similar entities.

There were 173 patients with primary gastroduodenal ulcers admitted to the Medical or Surgical Services of The Mount Sinai Hospital during this time interval. The total number of admissions in this group was 228. Cases in which the x-ray examinations were doubtful were not included even though the clinical history was characteristic. Patients with gastrojejunal ulcers or with a history of previous operations on the stomach or duodenum were also omitted. These patients present a problem which requires separate analysis. Wherever possible, only readmissions for symptoms primarily related to the ulcer were included in this survey. Twenty-seven patients had two admissions; fourteen, three admissions; four, four admissions; three, five admissions; five, six admissions; and one, seven admissions.

Sex incidence. This group of 173 patients included, 141 men and 32 women. This represents a ratio of approximately four and a half men to one woman, an incidence comparable to that reported in other series. In the group of gastric ulcers the proportion of women was slightly higher. This may be due to the smaller number of cases rather than to any actual difference in incidence.

A glance at Table I will reveal the number of patients in each decade. It is readily understandable that the great majority fall into the sixth decade, yet there remains a sizable proportion of patients in the seventh and eighth decades, comprising in all 67 patients or approximately one-third of the entire group. It is fair to assume that as time passes more and more patients with ulcer problems will fall into the group under discussion because of an increased life span as proven statistically and the established tendency of ulcer to be a recurrent chronic disease.

Duration of symptoms. The symptoms in this group were typical of ulcer. Pain was the outstanding manifestation and was present even when vomiting, the result of obstruction, or bleeding in the form of hematemesis or melena, was the presenting symptom. In a number of instances the chief presenting complaint was apparently in the nature of an acute exacerbation of brief duration. A careful review of the history yielded sufficiently accurate information to denote the pre-existence of ulcer symptoms for years prior to the hospital admission. In almost a half of the duodenal ulcers, symptoms of the disease first manifested themselves after the age of fifty. In appreciably more than a half of the cases the symptoms in the gastric ulcer group also appeared after fifty years of age. The group is too small to permit a more detailed analysis but the evidence

TABLE I

Age incidence

AGE	MALE	FEMALE
years		
50–60	85	21
60–70	46	8
70–80	10	2
80 and over	0	1

TABLE II

Age at onset of symptoms

AGE	DUODENAL ULCERS*	GASTRIC ULCERS
Before 50 years	68	15
After 50 years	65	24

* In one case the data were missing.

is sufficient to state that it is not unusual for the initial symptoms of gastric ulcer to appear in the seventh and eighth decades of life. Likewise, an unusually large number of duodenal ulcers first manifest themselves clinically between the ages of sixty to seventy years.

Of the entire group (Table III) a large proportion of the patients had symptoms of relatively long standing. This was anticipated in view of the age group as a whole and the fact that these patients comprised the more recalcitrant ones requiring hospitalization. It was of interest that many patients commencing with ulcer symptoms after the age of fifty years had long standing symptoms before non-ambulatory therapy was instituted.

It is readily discernible that most of the patients presented long standing

ulcer histories. This was also true of most patients whose initial admission antedated their fiftieth year as well as of the larger group who were admitted for the first time after this age. This point serves to emphasize the chronicity of ulcer in certain individuals as well as the recurrent nature of the disease. An analysis of the duration of symptoms in each age and ulcer group (gastric and duodenal) might have been of value but this series seemed too small to justify such detailed study and it is questionable whether the findings would have differed greatly.

In the group of patients who underwent surgical intervention it is natural that extreme conservatism should have been exercised. This is noted in Table IV which shows the duration of symptoms in the surgical as contrasted to the non-surgical cases. It will be noted that the great majority of surgical patients were subjected to operative intervention after long periods of ulcer symptoms; in over two-thirds of these cases symptoms persisted for years. It was usually some complication or threatened complication that hastened the decision to resort to surgery in

TABLE III

*Combined statistics for cases of duodenal and gastric ulcers**

Symptoms of less than 1 year	36
Symptoms of from 1 to 5 years	32
Symptoms of from 5 to 10 years	38
Symptoms of from 10 to 20 years	45
Symptoms of 20 years and over	18

* In a few cases it was impossible to determine the duration of symptoms.

that third of the cases in which the symptoms were of a relatively short duration and in some with symptoms of longer standing.

Complications. It was to be expected that because of the age groups under consideration, the most frequent complications of ulcer such as hemorrhage and obstruction, should occur in a relatively greater proportion of cases in this series than are usually encountered. Approximately one out of five patients had clinical or x-ray evidence of obstruction. The degree of obstruction was by no means of uniform severity. In some cases, it was of short duration yielding to medical management; in others it was unyielding and resulted in marked loss of weight, dehydration and alkalosis. In a number of instances, temporary gastric compensation was of short duration and the patient was subsequently readmitted with complete retention. Bleeding, either in the form of hematemesis or melena, occurred in 45 patients, in approximately 25 per cent of the group. This incidence corresponds closely with the findings in a previous study by Manheim and Crohn (3) of a much larger series of cases including all age groups. Four patients, approximately 9 per cent of those who manifested

a bleeding tendency, died of hemorrhage, constituting only 2.3 per cent of the entire series. Bleeding was found to be relatively more common in those of more advanced age (Table V), but it should be borne in mind that the larger number of patients treated were in their sixth decade.

The four deaths included two of each sex. Two were men between the ages of 50 and 60 years. One woman succumbed in the same age period

TABLE IV

Duration of symptoms classified as to operated and unoperated cases†

DURATION OF SYMPTOMS	SURGICAL CASES	NON-SURGICAL CASES
Less than 1 year	8	28
From 1 to 5 years	11	21
From 5 to 10 years	16	22
From 10 to 20 years	12	33
20 years and over	8	10

† In four cases the duration of symptoms was unstated.

TABLE V

Table showing age groups with bleeding

AGE	MEN	WOMEN
years		
50–60	12	7
60–70	16	3
70–80	4	3

TABLE VI

Type of operation and age group in which operation was performed*

AGE	MEN		WOMEN	
	Partial gastrectomy	Gastro-enterostomy	Partial gastrectomy	Gastro-enterostomy
50–60	23	10	3	2
60–70	3	5		
70–80		2		

* In three cases the lesion was undisturbed.

and one between the ages of 60 and 70 years. It has been hypothecated that the prognosis of bleeding in the older age groups was worse because of the lack of resistance to acute blood loss and to the tendency of arteriosclerotic vessels to remain open in the ulcer base. While the mortality proved no higher than usual in this group, it should be noted that the bleeding was not of dramatic proportions in a number of cases. Acute

gastric and duodenal perforations were not considered. This study was reserved for chronic ulceration and as such it occupies an entirely separate niche in the ulcer problem.

It is surprising how frequently conditions incident particularly to this age group both accompany and complicate the ulcer status. The whole gamut of geriatrics could be surveyed if mention were made of only a few of the attendant conditions. Coronary artery and prostatic disease, diabetes and hypertension were the conditions most frequently responsible for hospitalization in the absence of ulcer symptoms.

Operations. In this group, fifty-one patients underwent operation for ulcer. Four patients underwent surgical procedures for other conditions at which time the ulcer was disclosed. It was natural that the greater number were carried out on patients between fifty and sixty years of age. This represents an operative incidence of approximately 30 per cent. It is fair to assume that only compelling circumstances, such as, intractable pain, pyloric stenosis, repeated episodes of serious bleeding, or evidence of a carcinoma on the lesser curvature of the stomach rather than an ulcer prompted operative intervention even in this small group. Table VI shows the age groups in which surgical intervention was undertaken and the nature of the procedure. The comparatively large number of conservative procedures bears witness to the conservative surgical attitude adopted in patients over 50 years.

The operative mortality in this series is naturally larger than for a comparatively lower age group. This raises the question of operative indication, a difficult question to settle dogmatically. Each case should be judged on its individual merits. Patients can be helped surgically in spite of a long standing, depleting illness and we know of no more gratifying surgical successes than those obtained in cases of complete pyloric obstruction with emaciation, azotemia and alkalosis. Aged individuals have successfully undergone surgical procedures under local anaesthesia with careful pre-operative preparation consisting of gastric lavage, repeated transfusions, the use of vitamins and heliotherapy. Recently it was noted that long standing obstruction tends to gastric atony which gastro-enterostomy does not immediately relieve.

SUMMARY AND CONCLUSIONS

1. A series of cases of gastroduodenal ulcers in patients over 50 years of age is discussed.
2. Gastroduodenal ulcer is frequently manifested first in old age.
3. The problem is aggravated by the frequency of complications as the result of long standing disease.
4. Surgery should be circumspectly employed but the results under

proper management are frequently satisfactory and in certain cases, exceptional.

5. It is reasonable to assume that because of increasing longevity more and more patients will require treatment for ulcer in the older age groups.

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PNEUMONIA WITH APICAL AND INTERLOBAR EMPYEMA

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During the latter half of 1913 Dr. Ira Cohen was House Surgeon on the Service of Dr. Lilienthal and I was his Senior Intern. One night I returned to the Hospital from the theatre, and on midnight rounds I saw a girl about 9 years old who had just been operated on by Dr. Lilienthal. The case was one of gangrenous perforated appendicitis with general peritonitis. The disease had been present for several days before the child came to the Hospital and when I saw her she appeared, in my judgment, moribund. Her temperature was high and her pulse very rapid and feeble.

That was before the days of simple transfusion and intravenous technique; before the day of Sulphanilamide. At that time such an operative wound was tightly sutured about a heavy thick walled rubber drainage tube. Fluid was sponged out of the peritoneal cavity instead of being removed by gentle suction. The margin of safety in this type of case was much narrower in 1913 than in 1940.

However, the little girl did not die. She remained in the Hospital for many weeks. She rode the storms of residual abscess and faecal fistula, but she rode them to a triumphant finale, and left the Hospital restored to normal health. I am sure that Dr. Lilienthal remembers that little Irish girl, whose first name was Margaret but whose surname I have forgotten. During her entire illness Dr. Lilienthal insisted with his characteristic optimism that the prognosis was splendid; that he "had seen much sicker cats get well."

I think that there is given to every physician an opportunity to enjoy the glow of satisfaction which comes when an apparently hopeless case recovered, and those episodes stand out as never forgotten landmarks on the panorama of his professional life.

The recovery of a patient ill of superlatively dangerous disease depends upon three factors: One is expert, accurate, and well timed therapeutics; another is the native resistance of the patient. The third essential is the same influence which is present when a 50 foot putt drops into the hole at the critical point of a tight golf match. This intangible element is called by the religionist "the Grace of God" and by the pagan—common barnyard variety of good luck.

It is such a case that I have selected to report. In consideration of Dr. Lilienthal's extremely active and productive interest in chest dyscrasia, I am delighted to dedicate this report to my former chief, whose teaching

and philosophy have been a life long source of professional help and personal pleasure to me.

CASE REPORT

History. The patient consulted me on February 11, 1937. She was then 33 years old, a business secretary by occupation. She had been ill for five days. The onset was with fever, cough, haemoptysis, and dyspnea. There were present the usual physical signs of pneumonia with a patch at the right base and one at the right apex.

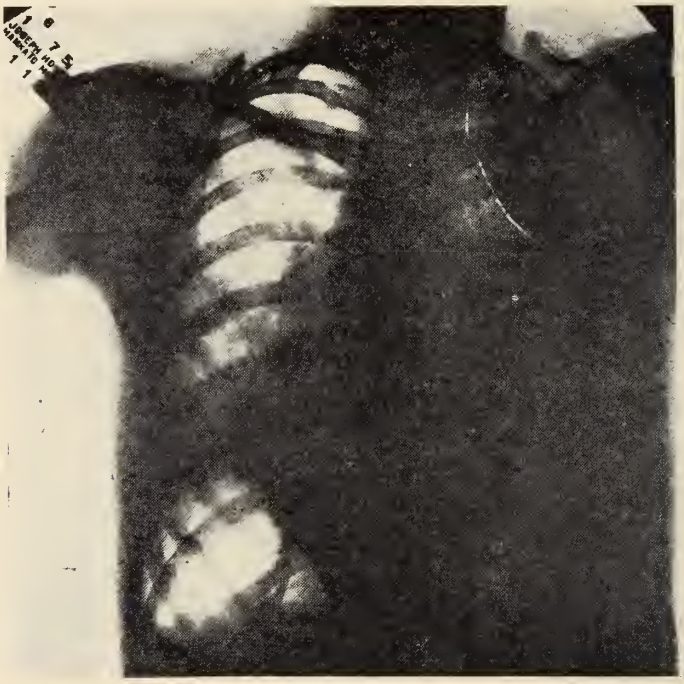

FIG. 1

The temperature was 99°F., the pulse was 130 per minute, and the patient appeared very toxic. The leukocyte count was 21,100.

She entered St. Joseph's Hospital, Mankato. X-ray examination of the chest disclosed a pneumonia at the right base and two separate small encysted effusions, one in the upper and one in the lower right chest.

Neufeld typing of sputum disclosed pneumococcus Type I. Accordingly, she was given 20,000 units Type I Pneumococcus Antiserum every six hours and was also given Prontylin, which was stylish in the treatment of pneumonia at that time.

On the following day exploratory aspiration was made in the second interspace anterior axillary line, and also in the fifth interspace, tapping both the encysted effusions. Thin seropurulent fluid was obtained in each instance. It was considered advisable to delay any surgical procedure.

On the next day the patient was given 300 cc. of blood by direct transfusion and the dosage of Type I Antiserum was altered from 20,000 units every six hours to 40,000 units twice daily, and continuous oxygen therapy was commenced.

Five days later she was again given a blood transfusion.

On February 20, which was about the fourteenth day of her illness, she became extremely toxic, and from that date through March 9 (17 days) this patient was, for all intents and purposes, moribund. Her memory was entirely obliterated for this period of time. Her pulse ranged from 120 to 140 per minute; her temperature to 105°F.; she was taking almost no food; she was very toxic. Fluids were supplied intravenously and blood by several direct transfusions. Coramine was given as a circulatory and respiratory stimulant, although I am very skeptical of the value of that type of medication.

Surgery. On February 24, the apical empyema was drained by intercostal puncture with a large trocar through which a tube was placed. The lower effusion (inter-

FIG. 2

lobar) was aspirated and 100 cc. of thin cloudy fluid removed by suction. This cavity did not refill and gave no further trouble. The upper encysted empyema gave considerable trouble. This was located directly in front of the scapula. The intercostal drainage was not functioning well, and on March 6, rib resection was accomplished just below the angle of the scapula. Through this opening a needle was introduced sharply upward in front of the scapula, entering the cavity. A large caliber tube was placed. Drainage was impeded because the scapula caused angulation of the tube and it was necessary to irrigate the cavity through the tube several times daily.

Course. On March 9, the thirty-third day of her illness, the patient displayed a spectacular improvement and from that date forward her progress was rapid and she left the Hospital on March 25.

During her illness she had 220,000 units of Pneumococcus Antiserum, six direct blood transfusions, 30 liters of glucose solution intravenously, 50 cc. of Coramine (of doubtful value), and 23 grains of morphine.

This patient was given no Sulfanilamide. At that time this drug was still in the experimental stage and the toxic effects were exaggerated in the literature. I was afraid of anything which might increase this patient's toxicity. Today one would unquestionably make use of this drug in such a case to great advantage. The patient had a rather long drawn out convalescence at home, but returned to work on June 1.[1]

DISCUSSION

The brilliant Neo-Pagan philosopher, Lin Yutang, in his essay "The Importance of Living" has said:

"I wake up in the morning and seem to hear some one in the house sighing and saying that last night some one died. I immediately ask to find out who it is, and learn that it is the sharpest, most calculating fellow in town. Ah, is this not happiness?"

I would like to plagiarize the style of Lin Yutang: To be the physician to a patient superlatively ill; to see him so overwhelmed by disease that he is relatively dead; to abandon hope for his recovery; to direct a total war of therapeutics against the enemy; to see this patient defeat death and become well again. Ah, is this not happiness?

[1] I am indebted to Dr. A. J. Wentworth, of Mankato Clinic, for x-ray interpretation, and to Dr. W. C. Stillwell, also of Mankato Clinic, for the surgical management.

The first x-ray plate is poor in quality because it was made with a portable bedside unit.

BENIGN ADENOMA OF THE BRONCHUS

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Benign bronchial adenomata present many features of theoretical and practical interest. The clinical manifestations, pathology and treatment have been described in detail previously (1, 2, 3, 4). In brief, these tumors may cause bleeding and bronchial obstruction with all its sequelae. This may simulate malignancy, or cause bronchiectasis, acute and chronic pneumonic processes and pulmonary fibrosis as well as "asthma" (wheezing due to partial obstruction). If the tumor is allowed to remain *in situ* and the suppuration persists for some months, secondary bronchiectasis and pulmonary fibrosis are frequent sequelae. These changes may be irreversible after a time and the pathologic alterations in the lung structures will persist. In an occasional patient, as in the case described here, these changes are not necessarily accompanied by any clinical symptoms. Most frequently, however, if the tumor is of long duration, the secondary pulmonic processes produce symptoms after the tumor has been removed.

CASE REPORT

History. A 33 year old woman was admitted to the private service of Dr. Howard Lilienthal on January 17, 1935 because of high fever of thirteen weeks duration and cough with expectoration, at times blood-tinged, for two and a half years. She had had "asthma" for several years and recently had lost a "great deal" of weight. She was referred to Dr. Lilienthal for pneumonotomy for relief of her symptoms. X-ray examination of the chest showed contraction of the left side and almost complete opacity of the left lung. The hemoglobin was 60 mg. per cent; the red blood count, 3,800,000; the leucocyte count (polynuclear neutrophiles, 85 per cent), 18,000. The temperature on admission was 102°F. Although the patient's physician believed her incapable of withstanding a bronchoscopic examination Dr. Lilienthal decided that she required this examination and referred her to me.

On the day of admission to the hospital, a bronchoscopic examination was performed. A large amount of non-odorous pus was evacuated from the left bronchus. There was a friable, readily bleeding, sessile growth in the left main bronchus just above the left upper lobe orifice. A large portion of the growth was removed. The clinical diagnosis was benign adenoma of the bronchus. There was immediate relief of symptoms, the fever and the cough disappeared. On microscopic study of the growth it was shown to be an adenoma. Two subsequent bronchoscopic examinations were performed at one week and at one month intervals for the purpose of completely eradicating the growth. There was no further appearance of pus at these examinations.

The remnants of the tumor were removed and the base was coagulated by means of diathermy. X-ray examinations performed two weeks after the hospital admis-

sion showed infiltration of the entire left lung and areas of bronchiectasis. The patient was discharged from the hospital as greatly improved. When seen several months later she was asymptomatic and there was no recurrence of her asthma.

DISCUSSION

An important aspect of benign adenoma is simulation of bronchial carcinoma. Approximately seven per cent of all the bronchial tumors which I have seen are benign adenomata. The rest of the tumors were malignant growths, with an occasional exception. Until Wessler and Rabin (1) reported the clinical and pathologic features of these adenomatous tumors they were always thought to be malignant and treated accordingly by extirpative surgery or by resignation. Even today, clinicians and pathologists erroneously diagnose these tumors as carcinomas and proceed along the lines indicated by this diagnosis. I have seen two such instances in the past few months.

Early and correct diagnosis results in the complete cure of the patient, without residual pulmonary changes. The treatment is bronchoscopic removal of the tumor, with adjuvant measures in some instances. These measures are most frequently surgical diathermy, occasionally implantation of radium or its derivatives and rarely external roentgen ray therapy.

A desperately ill patient, who was advised to undergo a hazardous major surgical procedure, was restored to good health in a short period of time by three bronchoscopic procedures under local anaesthesia. In addition, "asthma" which had been present for many years, disappeared with the removal of the tumor. The clinical insight and the surgical judgment of Dr. Lilienthal were the deciding factors in the salvation of this patient.

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BERNARD-HORNER SYNDROME, AS A COMPLICATION IN CHEST OPERATIONS

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With the advance of surgery into virgin fields, new procedures are invented, previously inaccessible organs and structures are attacked and new complications and sequelae are encountered. As our knowledge of these unfavorable complications increases, and as our experience in the new fields of endeavor becomes more extensive, we gradually learn the whys and wherefores of these conditions. Increased knowledge and experience will enable us to determine which of them are avoidable and what procedures are to be followed in order to prevent their occurrence.

Bernard-Horner syndrome is not a new phenomenon. It was fully described by Claude Bernard (1) in 1852 and by Horner (2) the ophthalmologist, in 1869. Numerous investigators have reported the development of this phenomenon in a fairly large variety of conditions, all of which had in common the involvement of the cervical sympathetic plexus. Tumor of the apex of the lung, tuberculosis of the apex of the lung, stab wounds and gun shot wounds of the neck, neoplasms of the cervical spine, etc. have been found associated with this phenomenon. Recently, however, we have had a rather unique experience in which this condition developed after operations upon the chest, where, as a result of the procedure, there occurred some injury to the cervical sympathetic structures. Before describing these cases, it might simplify matters somewhat to describe, quite briefly, the anatomy of the cervical sympathetic nerves and the pathogenesis of the symptoms produced.

In his description of the method of production of the Horner syndrome, de Jong (3) says, "It is now known that Horner syndrome follows injury to or disease of the brain stem, (floor of 3rd ventricle and medulla) lower part of cervical or the upper part of the dorsal portion of the spinal cord or its nerve roots, the superior cervical sympathetic ganglion or the post ganglionic nerves." Higgins and Kraus (4) "express the belief that the motor portion of the syndrome, which consists of ptosis, miosis, and enophthalmos, is always present, while the vasomotor, trophic, and secretory disturbances are present only with more extensive lesions. Miosis, probably the most common feature, is due to loss of the sympathetic stimuli to the radiating dilator muscle fibres of the iris, with the unopposed parasympathetic stimuli acting on the sphincter pupillae. The pupil reacts

weakly to light and in accommodation, but it does not respond to the instillation of cocaine, and the cilio-spinal reflex is lost. Ptosis, the next most common finding, is not a true palsy of the eyelid due to involvement of the levator palpabrae superioris muscle but rather is a pseudo-ptosis due to loss of sympathetic innervation to the tarsal muscle. The patient is able to lift his eyelid voluntarily. The mechanism of enophthalmos, the third motor symptom, has not been satisfactorily explained. It is considered by most authorities to be due to palsy of the orbital or retrobulbar muscle of Müller. Others believe the enophthalmos to be on a trophic basis, associated with a decrease of the orbital fat. There is also some difference of opinion as to whether the retraction of the eye ball is real or apparent, as the narrowing of the palpebral fissure gives the illusion of enophthalmos. The remaining constituents of the syndrome of involvement of the cervical portion of the sympathetic system are less constant. Ipsolateral dilatation of the vessels of the head, neck, conjunctiva and upper extremity is seen, and this is, of course, due to the paralysis of the sympathetic supply to this region. On the same basis, but occurring less commonly, homolateral anhydrosis is observed. Secondary to these factors, hyperemia and higher temperature of the skin occur in these regions. The fact that certain of the constituents of the typical Horner syndrome occur in some cases and not in others may be due to the area of the nervous system involved. It is now believed that the fibres controlling oculo-pupillary action arise in the 8th cervical and 1st dorsal segments of the spinal cord, while the vasomotor, trophic and secretory nerves arise from the 2nd to the 6th dorsal segment. A lesion might involve one set of fibres without affecting the others. Also in the case of injury to the preganglionic and postganglionic sympathetic nerve fibres, certain fibres may be destroyed while others escape. Cobb and Scarlett (5) found that "injuries to the 7th and 8th cervical and 1st dorsal nerve roots produce the most complete and most severe oculo-pupillary syndromes, that injuries to the cervical portion of the sympathetic trunk are followed by less severe symptoms, and that definite injuries to the spinal cord produce the least pronounced phenomena."

The following cases were operated upon in the Montefiore Hospital—Division of Tuberculosis (Dr. Harry Wessler—Director) and Division of Surgery (Dr. A. A. Berg, Director).

CASE REPORTS

Case 1. History. (Adm. 29364.) A. K. was admitted to the Montefiore Hospital August 14, 1936 with a diagnosis of bilateral pulmonary tuberculosis with cavitation. On April 15, 1937, a left intrapleural pneumonolysis was performed. Three string adhesions and one broad band adhesion were seen at the apex of the lung running upwards and inwards. These were severed by the galvano-cautery without any technical difficulty. On the following day, a typical Horner syndrome was noted on the left side. The patient was seen by the neurological consultant, Dr. M.

Kesehner, who stated, "The patient had no Horner syndrome before operation. Present condition must be due to some interference with the sympathetic plexus on the left side. Whether this is coincidental or due to some manipulation on the left side of the neck during surgical procedure cannot be definitely determined. The temporal relationship of the appearance of the Horner syndrome and the operative procedure suggest the former to have been produced by the latter. Left pupil failed to react to instillation of 1 per cent cocaine hydrochloride. Right pupil reacted normally with dilatation."

An extremely intense subcutaneous emphysema was noted of the anterior chest wall, neck and left upper extremity.

On April 20, 1937 she was again seen by one of the neurological consultants, Dr. I. S. Weehsler, who found that, "The Horner syndrome apparently is receding since the left pupil is no longer contracted though still smaller than the right. Evidently there has been involvement of the cervical sympathetic. It is difficult to conceive of a direct injury to the ganglia or chain from manipulation in the pleural cavity however near the apex that might have been. We must assume that the mechanical effect of the emphysema deep in the tissue was the cause of the acute onset of the Horner syndrome. Its improvement also speaks for a temporary effect. If the hoarseness is the result of involvement of the recurrent laryngeal nerve we must further assume damage to this nerve. The proximity of the latter to the apex could speak for direct damage but here too the mechanical effect of the emphysema could be direct cause."

The subcutaneous emphysema gradually subsided and was entirely gone within a week but there was no change in the ocular condition. The tuberculous process spread rapidly and the patient developed a terminal tuberculous meningitis and died on June 5, 1938. The Horner syndrome persisted up to the time of death.

Case 2. History. (Adm. 25919R.) C. N., 42 years old, was admitted to the Montefiore Hospital March 5, 1937 with a diagnosis of right pulmonary tuberculosis with cavitation and right encapsulated pyopneumothorax. On April 22, 1937 a typical first stage thoracoplasty was performed. The first and second ribs were removed up to the costal cartilages and a segment of the third rib about seven inches long was removed. A Semb apicolysis was done at the same time. The apex of the lung was densely adherent to the neuro-vascular structures. These adhesions were dissected free by sharp and blunt dissection and the apex could be seen to drop free as the last of the adhesions was severed. Two days later, April 24, a definite Horner syndrome was noted on the right side, as evidenced by miosis, enophthalmos and ptosis. The pupil reacted to light and in accommodation and failed to react in the usual manner to instillation of cocaine hydrochloride. This condition remained unchanged during his stay in the hospital and was still present when seen in the follow-up clinic in July, 1938.

Case 3. History. (Adm. 28810.) A. W., 39 years old was admitted to the Montefiore Hospital September 23, 1936 with a diagnosis of chronic tuberculosis of left upper lobe with cavitation. On October 25, 1937 a first stage thoracoplasty with Semb apicolysis was performed. The first and second ribs were removed subperiosteally up to the costal cartilages and a segment of the third rib, seven inches long, was removed in the same manner. Firm, fibrous, bands held the apex of the lung closely attached to the brachial plexus and large subclavian vessels. These bands were severed by sharp and blunt dissection and as the last attachment was cut through, the apex of the lung could be seen to drop free.

On November 1, 1937 a definite left Horner syndrome was noted. There was enophthalmos, ptosis and contraction of the pupil. The latter reacted to light and

in accommodation. There was no anhydrosis or flushing on the left side of the face. This condition persisted up to the time of her discharge from the hospital and when seen in the follow-up clinic October 2, 1938 it was still present.

SUMMARY

The development of a Horner syndrome is described as a post-operative complication following a thoracoplasty and Semb apicolysis in two cases, and an intrapleural pneumonolysis in a third case. The condition was permanent in these three instances and was most likely brought on by an injury to the cervical sympathetic nervous system at the time of operation. Since the same technique was employed in all thoracoplasties and pneumonolyses performed in approximately 150 other patients, without this complication, the question that presents itself is whether in these three instances, the apparently injured portion of the sympathetic system may not have been situated outside of its usual location and thus within the area of the operative field subjecting itself to unavoidable trauma.

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PSORIASIS WITH TUMOR-LIKE FORMATIONS

Observations over a Twenty Year Period

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Although the literature contains numerous reports of the various forms in which psoriasis manifests itself, a repeated and careful check of the recorded cases has failed to unearth any case similar to the one described in this report. This patient has been under continuous observation for over twenty years (1) and has been presented before several medical and dermatological societies. During this period of time, the case has been carefully studied and numerous investigative procedures have been performed, in attempts to determine an etiological factor and to obtain an effective therapeutic agent.

This type of psoriasis bears a remarkable clinical resemblance to other dermatoses, as well as to other forms of psoriasis. It simulates in appearance parakeratosis ostracea (scutularis), mycosis fungoides, psoriasis rupioides, psoriasis verrucosa, and arsenical dermatitis, and in many ways suggests sarcoma, especially Kaposi's hemorrhagic sarcoma. However, repeated studies of the skin of this patient, in addition to microscopic examinations of the tissues, reveal differences which clearly prove that this case is not related to any of these dystrophies.

The clinical recognition of typical psoriasis is not difficult. It depends on such definite data as the occurrence of a slightly elevated, thickened or infiltrated, papular lesion with sharply defined borders, located on characteristic sites, and covered with shiny, silvery-white scales, which, on removal, reveal bleeding points and inflammatory bases. However, this most obstinate of all dermatoses may present so may different appearances, that even the experienced dermatologist may find it difficult to make a correct differential diagnosis. The subclassification of the disease according to its many manifestations and distinctive features aids materially in arriving at a correct diagnosis. Various terms such as punctata, guttata, nummularis, circinata, diffusa, follicularis, and gyrata have been applied to the different types of psoriatic lesions to designate in a word their size or configuration. Although the size of the lesions varies and individual patches and discrete lesions are commonly observed, the eruption may often be so diffuse and confluent as to cover the entire cutaneous surface. This is the rarely observed universal type of psoriasis. However, in all these different forms of the disease, although the clinical pictures

differ widely, the histopathologic evidence is at all times characteristic of psoriasis.

This case illustrates the rarely observed, universal type of psoriasis. It is unique in that it presents in association with the disease the hitherto undescribed feature of tumor formation.

CASE REPORT

History. (Adm. 21771.) L. G., a 21 year old white girl was first seen at the Skin Department of The Mount Sinai Hospital in March, 1919 (Fig. 1). She complained of a recurrent persistent eruption of the entire body of three years' duration. There was no history of childhood illness, of nervousness, diarrhea, gastric disorder or endocrine abnormality.

The eruption had always been more or less generalized and accompanied by slight itching. It had appeared first in the form of red, scaly patches behind both ears, and then had spread rapidly to the scalp, and more slowly over the entire body. At first, the patient continued to attend school, but finally had to leave because her entire face and skin became involved. On her first visit to The Mount Sinai Hospital dispensary, she was observed to have a universal redness of the skin with discrete and confluent papular lesions, forming large patches and virtually covering the entire cutaneous surface. She was transferred to The Mount Sinai Hospital and admitted, on March 26, 1919, to the service of Dr. Herman Goldenberg, who confirmed the diagnosis of universal psoriasis. Treatment consisted of inunctions with chrysarobin ointment. She showed slow improvement, but subsequent to autoserotherapy, the lesions involuted rapidly, and she was discharged, on May 24, 1919, with only slight erythema and scaling.

The patient stated that subsequent to her discharge from The Mount Sinai Hospital she felt considerably better for several months. However, the eruption began to reappear gradually, and was associated with intense itching. It became progressively worse until her admission to the Cornell Skin Clinic in 1923.

Examination (1923). The patient had a regular pulse rate of 88 per minute and a temperature of 98.4°F. The systolic blood pressure was 104 and the diastolic pressure was 68 mm. of mercury. There were no tremors of the hands or tongue, no exophthalmos and no enlargement of the thyroid. The pupils were equal and reacted to light. The examination of the heart and lungs disclosed no abnormalities. The reflexes were normal. The body had a musty odor. Examination of the skin revealed a universal eruption made up of large, confluent patches, which covered the entire trunk and upper extremities, except for small scattered areas of apparently normal skin on the upper part of the arms and in both axillae. The skin in these areas was livid red, thickened, lichenified and covered with shiny, white and yellowish-white, fine and heavy scales. When these scales were removed, the underlying skin revealed the characteristic bleeding points of psoriasis. On the greater part of the dorsa of the hands and fingers, similar lesions were present. The palms were only slightly reddened and revealed thickening of the skin with loss of elasticity as well as numerous elevated, scaly, hyperkeratotic papules about 2 mm. in size. The face and neck were almost entirely covered by one large, confluent, bright red, shiny patch, which was sharply demarcated from the surrounding skin. Small islands characteristic of psoriasis, and varying in size from 1 mm. to 2 mm., were surrounded by this main patch. The eruption also extended along the thighs, but as it approached the antero-medial border, the diffuse areas gave way to large, linear, reticulated patches, which were livid red in color, elevated, sharply demarcated, and covered with thick, dirty-white scales and heavy, yellow crusts. These patches were firm

in some areas but doughy and elastic in others. On both legs, in the region of the knee, there were infiltrated, lichenified, lurid red patches.

The most unusual feature, however, was observed on both legs (Fig. 2). On these sites, both anteriorly and posteriorly, there were innumerable tumors varying in size from 1 to 4 cm. These growths were distinctly elevated about 1.8 cm. above the surface of the skin. They were rounded, oval, flat and regular and were dark red in color. Many of the growths were covered with dirty-white scales and thick layers of yellow crusts. The skin underneath the crusts was smooth, shiny and red. Besides these distinct tumors, there were numerous tubercles and infiltrated plaques. These tumor-like lesions were firm and hard. On the backs of the legs there were large, confluent, infiltrated plaques. The surfaces of these lesions were not ver-

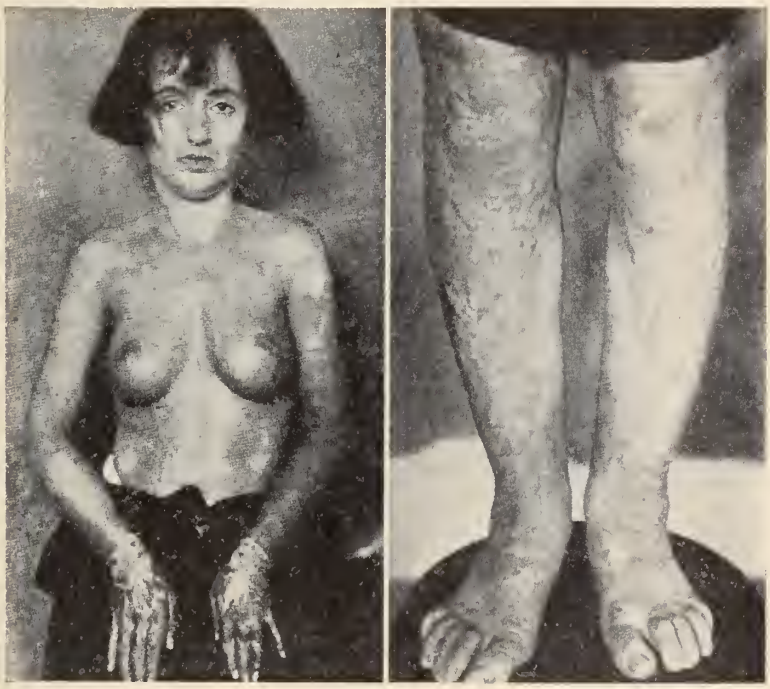

Fig. 1. Left. Universal erythroderma of the skin, in 1924
Fig. 2. Right. Tumor-like infiltrations of the legs (1924)

rucous in nature, but were rather smooth and shiny when the crusts and scales were removed. The plantar surfaces of the feet showed callosities and hyperkeratotic papules. On the dorsum of the toes there were small infiltrated tubercles. The nails of the toes were dry, yellowish, friable and scaly, while those of the fingers were dry, only slightly discolored, and stippled. The scalp was red, edematous, and covered with yellow crusts. The hair was of normal distribution, but the outer third of the eyebrows was absent. The lips were dry, thickened, scaly and fissured, and the infiltrated patches of the skin seemed to spread over the vermilion.

In summary, the cutaneous manifestations which this patient presented, consisted of universal psoriasis associated with: (1) hyperkeratoses and callosities of the palms and soles, (2) infiltrated plaques and strands on the thighs, (3) tumor-like growths on the legs, (4) involvement of the lips and (5) involvement of the nails.

Laboratory Data. The urine examination showed no abnormal findings. The Wassermann reaction was negative. The hemoglobin was 90 per cent, the white blood cells, 8000. The differential count was normal except for a 3 per cent eosinophilia. The blood chemistry showed 100 mg. per cent of glucose; 24 mg. per cent of nonprotein nitrogen; 12 mg. per cent of urea-nitrogen; 2.5 mg. per cent of uric acid; and 0.7 mg. per cent of creatinin. There was an increase in the basal metabolic rate of 43 per cent. During the entire examination the patient was very nervous and frequently had involuntary tremors. Because of this high basal metabolic rate, and the absence of clinical signs of hyperthyroidism, the basal metabolism test was repeated, with a similar result.

Histopathology. In order to study the pathology of the different types of lesions presented, sections of skin were removed from various sites, including the typical

FIG. 3. Tissue from tumor-like formations of leg, hyperkeratosis and parakeratosis of the stratum corneum, papillary and subpapillary cellular infiltration.

psoriatic patch on the trunk, the strandlike, infiltrated lesions on the thighs, and the tumor-like growths on the legs. Examination of the tissue removed from the tumor on the anterior aspect of the leg showed changes in the epidermis (Fig. 3). The corium showed essentially cellular infiltration, most marked in the papillary bodies, and to a lesser degree in the subpapillary areas. Edema was also present and the blood vessels appeared dilated. A more detailed study of the tissue showed a thickening of the stratum corneum with hyperkeratosis and parakeratosis. The layers of scales so produced were wavy in character and the outermost layer of cells was flattened and stratified. Beneath this layer, the cells were slightly larger, edematous, and stained poorly. The stratum granulosum was normal. In the rete there was intercellular and intracellular edema. Wandering cells could be seen, and minute abscesses (Munro's abscesses) were evident. The epidermis was very much thickened because of the hypertrophy in the rete, but this was confined almost completely to the rete pegs. The acanthosis consisted mainly of an elongation of the rete pegs. In the corium, the edema and cellular infiltration was marked. The

collagen bundles were swollen and enlarged, and the individual fibers stained very poorly. The infiltration was most marked in the papillary bodies, especially around the dilated blood vessels, and consisted of fibroblasts, leukocytes and large, round cells containing nuclei. The infiltration was most marked in the uppermost parts of the corium, but also occurred in the subpapillary regions. Here again, it consisted of the same types of cells and was most prominent around dilated blood vessels and hair follicles. The blood vessels were dilated and the endothelial cells were distended. The acanthosis and infiltration were less intense in tissue removed from the strands on the thighs than in the tissue from the tumor-like growths. The tissue from lesions on the trunk was histologically similar to the tissue from the thighs.

Treatment. The patient was given no internal medication, and for local therapy she was directed to use simple emollients. Fractional doses of roentgen rays to the various parts of the body were administered at weekly intervals from April 17, 1924. This was continued until October 1924, but since it afforded no relief and no change, abandonment of this form of treatment was deemed advisable. During this period, the pruritus had become most intense. About the middle of October 1924, the patient requested hospitalization stating that nothing had given her such relief as she had experienced from autoserotherapy.

She was therefore admitted to the Beth Israel Hospital. On admission (October 1924), her cutaneous condition was primarily the same as it had been at the time of her first visit to the Cornell University Medical College Clinic, except for the fact that the heavy scales and thick crusts had disappeared with the use of emollients. During her stay in the hospital the patient received ten injections of autoserum. The amount of blood withdrawn varied from 50 to 60 c.c. and the amount of serum injected varied from 20 to 28 c.c. These injections were given at intervals of five days. She was discharged on December 8, 1924, with marked improvement in her skin condition. The skin was white and smooth; the neck and trunk showed only scattered, small, red patches. The nodules and tumor-like growths had almost completely faded. In those areas where there had been infiltration, the lesions had become flat, smooth, and free of crusts and scales. The face and upper part of the trunk were practically free from lesions. The tubercles and tumors of the lower extremities had flattened and many had disappeared.

One month later, however, (January 2, 1925) the patient presented herself for an examination and the lesions were found to be recurring in the form of small, pea-sized, elevated, round papules on the face and forearms. By January 30, 1925, there was more marked involvement of the skin, the condition becoming very much worse in the next three days. At this time a generalized erythrodermia with exfoliation appeared, and the tumors of the lower extremities recurred. The patient was given six intramuscular injections of 10 c.c. of her own blood at weekly intervals. Three days after each injection, the patient stated that she felt warm and slightly dazed. When last seen in 1925, her skin was less infiltrated but the tumors were practically unchanged.

Interval History. From 1925 to the present time, the patient has been under continuous observation both in the Out-Patient Department and in The Mount Sinai Hospital. She was admitted to The Mount Sinai Hospital on four subsequent occasions, and during one of these periods (1934) remained in the hospital for more than one year. The many additional clinical and laboratory examinations which have been performed can be summarized as follows:

(1) *Basal metabolic rate.* Determinations of the basal metabolism on numerous occasions were consistently above plus 30 per cent and were even as high as plus 47 per cent in 1935. This elevation of the metabolic rate without symptoms of

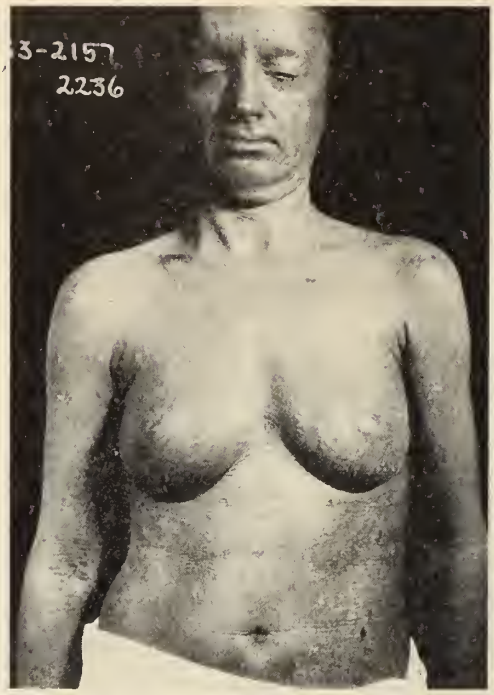

FIG. 4. Universal erythroderma (1940)

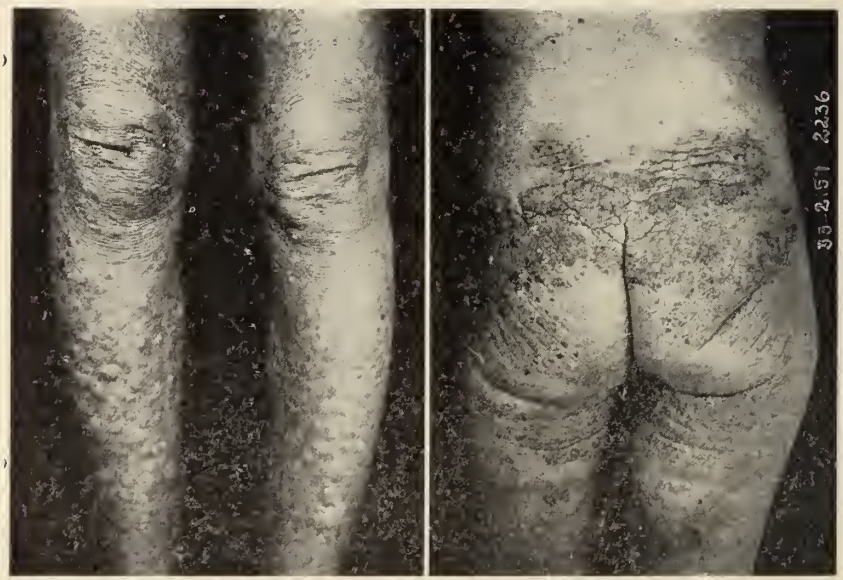

FIG. 5. Left. Tumor-like formations of the legs (1940)
FIG. 6. Right. Infiltrated plaques on the buttocks (1940)

hyperthyroidism is probably attributable to changes in sweat function and in heat radiation.

(2) *Skin temperature.* The temperature of the skin surfaces has been taken on several occasions always proving to be above the normal figure for the regions tested. In October, 1936, with a room temperature of 25.7°C., the temperature of the forehead was 33°C., the epigastrium 33.6°C., the fingers 31°C., and the toes 26.5°C. In April, 1937, the temperature of the forehead was 33°C., the epigastrium 33.7°C., the fingers 31.5°C., and the toes 26.2°C.

(3) *Histology.* Histological examinations of the nodular growths have been repeated on several occasions. In 1934, a biopsy showed wild down-growth of epidermal tissue in irregular strands extending deeply into the cutis. The cells varied in size and shape and showed many mitotic figures. There was definite pearl formation and the lymph spaces showed infiltration. The cutis was the site of a marked cellular reaction. On the basis of the above findings, a diagnosis of epithelioma was made. In December 1939, a section was taken from a nodular lesion on the buttocks. This section showed marked proliferation of the epidermis with numerous Munroe abscesses. There was marked proliferation of the fibrous tissue directly beneath the acanthotic epidermis somewhat resembling the structure of a fibroma but with no definite capsule. The blood vessels in the deeper part of the cutis were dilated. There were no changes in the secondary skin appendages. Other sections showed nodular psoriasis or fibromatous nodules with overlying psoriasis. There was no evidence of epitheliomatous change as had been observed five years previously.

(4) *Therapy.* The patient received numerous forms of treatment during the twenty-year period with slight or no response. The nodular lesions have remained comparatively unchanged throughout the years. The only remission ever obtained followed autohemotherapy in 1924. In 1934, she received hyperthermic treatments with slight improvement.

(5) *Examination (1940).* Examination of the skin in March, 1940 showed universal erythrodermia with marked scaling (Fig. 4). Slight, diffuse alopecia of the scalp was present, and the eyebrows were absent. On the legs there were numerous oval, nodular masses about 3 to 5 cm. in size, some of which were pale white and others pink in color (Fig. 5). Several of these masses were superficially eroded and covered with a yellowish crust. A few smaller nodules had appeared on the thigh and there was a crusted, nodular lesion 2 by 2 cm. in size, on the right buttock (Fig. 6).

DIFFERENTIAL DIAGNOSIS

The fact that this patient had an universal eruption of psoriasis in 1919 six years before, with the subsequent development of tumors, led some of the dermatologists who first saw her to believe that the previous eruption had been a premycosis fungoides, and that she then developed the tumor stage of that disease. The passage of time has refuted that diagnosis. Because of the strong resemblance which this eruption bears to other cutaneous conditions such as parakeratosis ostracea (scutularis), keratosis produced by arsenic, psoriasis verrucosa, Kaposi's sarcoma, pityriasis rubra pilaris and leukemia cutis, it is deemed advisable to mention the distinquishing features which remove these conditions from final consideration.

Mycosis fungoides. Although the history and clinical picture of the cutaneous eruption of this patient might easily have justified a diagnosis

of mycosis fungoides, the histopathology at all times excluded such a possibility. The marked tumor-like infiltration of multiform cells, the broken-down protoplasmic masses in the lymph spaces, and the extensive mitoses, which are so characteristic of mycosis fungoides, were not evident in the tissue of this patient. Other factors also led to the exclusion of this diagnosis. The deep nodules which appear in mycosis fungoides eventually become elevated and enlarged, and then either disappear only to recur in other sites, or else begin to ulcerate. In the case of this patient, the tumors persisted on the legs without occurring on any other site for twenty years. After that interval, a few lesions developed on the buttocks. In addition, the color of the skin in mycosis fungoides is a dark, reddish purple, and itching is intense. In this patient the lesions were light red and the itching was slight in comparison. A final point, which would aid in excluding mycosis fungoides, is the fact that this patient did not respond to roentgen-ray therapy. The lesions of mycosis are extremely radiosensitive.

Parakeratosis Ostracea. The clinical and pathologic findings in this patient are unlike those observed in parakeratosis ostracea (scutularis). The picture of non-itching, oyster-shell-like formations, cuplike in appearance with tapering margins, from 0.8 to 1.2 cm. in thickness, which, when removed, reveal no bleeding points but merely a denuded skin suggesting the appearance of a nipple, as well as thornlike horny cones projecting into the pilosebaceous follicles, differs completely from that seen in this patient. In this case, the horny layers of skin, which compared to the oyster-shell-like formations, were entirely superficial, itched only slightly, and when removed, revealed not thornlike cones, but bleeding points on a convex or flat surface; a picture typical of psoriasis. Furthermore, the curled hairs contained in the oyster-like-shells and the oily, greasy appearance of parakeratosis ostracea were entirely absent in this case. The scales and crusts on the solid tumor elevations of this patient were only secondary factors easily removed by emollients and not at all resembling the whitish and yellowish laminated masses made up of crusts and scales which typify parakeratosis ostracea.

Keratosis produced by Arsenic. This patient showed none of the symptoms commonly associated with keratoses caused by arsenic. There was no pigmentation, no diarrhea or evidence of neuritis, and no arsenic was found in the urine at any time. Moreover, the lesions after having cleared up, recurred while the patient was under observation, and no arsenic had been applied locally or administered internally.

Kaposi's Sarcoma. In addition the fact that Kaposi's sarcoma is a disease more common to the male sex in the fifth and sixth decades, its pathological picture varies widely from that seen in this case. The small mushroom-like, livid and almost purplish-black tumors of this disease often appear pedunculated and show a tendency to hemorrhage and occasionally

to ulceration. The pigment and infiltrations are also of a hemorrhagic nature. These characteristic features were entirely lacking the case described herein.

Psoriasis Verrucosa. The dry, warty appearance and papillary hypertrophy of the lesions of psoriasis verrucosa are entirely unlike the firm doughy, infiltrated, tumor-like formations seen on the legs of the patient here presented.

Pityriasis Rubra Pilaris. Pityriasis rubra pilaris is a chronic skin disease characterized by small, horny, follicular papules and scaling, erythematous patches. Like the case described, the eruption may be universal and remain stationary for years and itching may be slight. However, were this disease present, the distinctive features such as the presence of follicular papules, especially on the backs of the fingers, the hyperkeratosis of the palms and soles would have been observed during the earlier stages of the eruption. Tumor formation has not been observed in pityriasis rubra pilaris.

Leukemia Cutis. The diffuse type of cutaneous leukemia more closely resembles the lesions with which we were confronted. This type is usually observed as a universal erythrodermia with secondary eczematization and lichenification. The hair and nails may shed. The lymph glands and spleen are enlarged. In contradistinction to the case described, however, pruritus is severe and the laboratory findings are frequently diagnostic.

SUMMARY AND CONCLUSIONS

A report is made of a case of universal psoriasis complicated by the presence of tumor-like lesions observed over a period of twenty years. The history and appearance of the lesions, when first described, suggested the possibility of mycosis fungoides, but a more detailed clinical study and microscopic examination of the excised tissue excluded this as well as other possibilities, such as psoriasis verrucosa, Kaposi's sarcoma, parakeratosis ostracea (scutularis), keratosis caused by arsenic, leukemia cutis and pityriasis rubra pilaris.

The tumors showed a pathology which differed in no way from that observed in a typical case of psoriasis; and the microscopic findings of the tissue from the general eruption and the infiltrated strands on the thighs were similar to those seen in the tumor growths, differing only in the degree of hypertrophy of the rete pegs, the infiltration and the intensity of the edema. The microscopic appearance suggested epithelioma on one occasion but further observation of the lesions made this diagnosis unlikely.

The strandlike, elevated infiltrations of firm and doughy consistency on the thighs and the involvement of the lips were also unusual features.

Arsenic may possibly have affected the original lesions by stimulating the tumor formations, but there was no strong evidence of this having

been the case. It is noteworthy that the characteristic clinical lesions and tumors both disappeared subsequent to autoserotherapy and that on cessation of this form of treatment, the lesions recurred. Autohemotherapy and hyperthermia caused a slight involution of the lesions, thus modifying the eruption, but no radical change was produced by these forms of treatment.

It is unfortunate that two decades have passed without the finding of a useful therapeutic agent. However, the patient is still living and the tumors, although disfiguring, have not affected her comfort or general well-being in any way.

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THE ROLE OF INTERNAL FIXATION WITH THE CORKSCREW BOLT IN INTERTROCHANTERIC FRACTURES

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Although internal fixation has yielded spectacular results with intracapsular fractures, this treatment applied to fractures of the trochanter merits an entirely separate evaluation. In spite of its anatomic proximity, the intertrochanteric fracture differs from the intracapsular lesion in a most important respect, i.e., its consistent favorable *local* response to conservative therapy. The trochanteric fracture almost always heals by bony union, whether plaster or traction is employed for treatment. Dissatisfaction with the conservative therapy of these lesions is not based upon unsatisfactory local results but upon the surprisingly high mortality rate which characterizes the fracture. Fractures of the trochanter are slow to heal and require a minimum of eight to twelve weeks before they are firm enough to permit discontinuance of immobilizing apparatus. The hazard of this type of therapy, particularly in the aged, is well known and its influence is reflected in the available statistical surveys.

Speed (1) in 1921 reported upon 118 intertrochanteric fractures treated conservatively at the Cook County Hospital. A mortality rate of 18.6 per cent was noted. Reggio and Wilson (2) found a mortality rate of 24.3 per cent in 62 similar fractures at the Massachusetts General Hospital. The most comprehensive recent survey is that of Key (3) who reviewed 214 fractures of the intertrochanteric type treated at the St. Louis City Hospital. The mortality rate in this large series of conservatively treated fractures was 38 per cent. In all of these reports, it is observed that the death rate is considerably higher than the severity of the original injury would indicate, and that it rises rapidly with the age of the patient. Moreover, if the causes of death are surveyed, it becomes apparent that a most important role is played by complications directly attributable to prolonged immobilization of aged patients.

From these observations it is evident that if results are to be improved, the long period of immobilization required by conservative therapy must be shortened in the elderly patient. Internal fixation of the intertrochanteric fracture is not concerned with the question of non-union. Surgical intervention is employed to decrease the period of inactivity and so avoid its hazards. As the statistics indicate, the need for operation occurs only in the elderly, or in those cases generally classed as poor surgical risks. It should be stressed that in young healthy patients who stand

bed rest with impunity, there is not the slightest statistical justification for internal fixation. In these patients, the risk of surgery, although small, considerably outweighs the danger of immobilization.

The early literature concerning internal fixation of fractures of the hip fails to accurately distinguish between intertrochanteric and intracapsular fractures, so that it is difficult to determine how extensively the intertrochanteric fracture has been treated by operation. Key reported on the use of the Smith-Peterson nail in these fractures and considered it useful. Most surgeons agree that attempts at fixation of these fractures with the nail have not yielded entirely satisfactory results. The Smith-Peterson nail constitutes insufficient support to maintain reduction without the help of a cervical stump attached to the distal fragment. When this is absent, as in intertrochanteric fractures, muscle pull rapidly forces the nail into *varus* position with consequent loss of reduction and separation of the surfaces of the upper fracture. To correct this defect, Thornton devised a supporting bracket which is attached firmly to the nail head and to the femoral shaft with screws and circumferential sutures. A similar apparatus has been recently presented by Dr. Wilson and his co-workers. Good results have been reported with both these devices which successfully maintain *valgus* position when properly applied. Their disadvantages are bulkiness and the major surgical task of their application. Because of these objections it appears unlikely that these inventions will prove suitable for routine use.

The principle of the corkscrew bolt is simpler and more directly applicable to fractures through the trochanter. When properly applied, the fragments are bound firmly together, and upward muscle pull on the shaft is converted into a force pressing the lower margins of the fracture surfaces against each other. To accomplish this objective, certain principles regarding the correct placement of the device must be observed. The corkscrew bolt is primarily an instrument of tension and will work most effectively if applied high and at right angles with the line of fracture. In this manner, the fracture segments that tend to separate most widely are bound together. The instrument requires a firm grip at both ends for proper function and the point of insertion cannot be higher than the level of firm cortical bone. Penetration should be sufficient for the corkscrew section to bite firmly into the bone of the femoral head, since the loose trabecular structure of the neck does not furnish dependable solidity. These principles must be separately applied with reference to the individual fracture.

The technic of application of the corkscrew bolt in intertrochanteric fractures differs in no important respect from that employed in intracapsular fractures and described in previous communications (4, 5). Reduction of the fracture must be maintained by traction while the device is being inserted. When the femoral shaft is split in the neighborhood of the

vastus ridge, the fracture hematoma may encroach on the operative site and cause troublesome bleeding. Once the hematoma has been evacuated, bleeding ceases promptly. When the instrument is well applied and the bone is firm there is no need for auxiliary postoperative fixation. After operation, a regimen of postural changes is immediately instituted. The positions are prone, supine, sitting up and lying on the sound side. During waking hours, the posture is changed at least every one and one-half hours and this is carefully controlled until the patient is freely able to move without assistance.

The following cases are intended to illustrate the mechanical adequacy of the corkscrew bolt in simple intertrochanteric fractures. By its use, immobilization was markedly curtailed and complete reduction was maintained until firm consolidation occurred. A comprehensive survey of the entire material will be submitted in a later publication.

CASE REPORTS

Case 1. History. (Adm. 435849). R. H., a 42 year old heroin addict, was admitted to The Mount Sinai Hospital, on February 5, 1939, directly after tripping on a door sill and falling on his right hip. X-ray examination confirmed the admission diagnosis of intertrochanteric fracture of the right hip (Fig. 1A). Internal fixation was chosen for treatment and on February 8, 1939, the fracture was reduced and fixed in position with the corkscrew bolt. Postoperative X-ray examination showed satisfactory position (Fig. 1B). No postoperative complications developed, the heroin addiction being satisfactorily controlled by morphine. On the eighteenth day after operation, the patient was able to lift his heel from the bed without pain, and three days later he was permitted to walk about with crutches without weight bearing. Weight bearing was instituted two weeks later and on March 23, the patient was able to use his injured leg almost as well as the normal one. X-ray examination at this time showed no change in position and beginning callus formation. He was discharged on March 27, 1939, walking without a limp but with a cane for protection. On examination four months after the injury there were no further complaints, no noticeable limp, and the patient was able to use both legs equally well. There was no measureable shortening or limitation of motion in the hip joint. X-ray examinations showed complete healing (Fig. 1C).

Case 2. History. (Adm. 450632). E. S., a 74 year old woman, had been a moderate invalid for several years because of severe arteriosclerosis, hypertension and polyarthritis. A residual malarial infection had caused intermittent illness for many years. She was admitted to The Mount Sinai Hospital on January 1, 1940 immediately after having fallen in her own apartment and being unable to rise. There was severe swelling and pain about the left hip. Shortening of one inch was present. X-ray examinations revealed an intertrochanteric fracture of the left femur with separation of the fragments (Fig. 2A). Because of the patient's general condition, internal fixation was decided upon for therapy and the operation was performed on the day of admission. X-ray examination revealed excellent reduction and fixation in good position with the corkscrew bolt (Fig. 2B). No postoperative fixation was employed. The postoperative course was complicated by persistent temperature elevation of unknown etiology, 102°F. for the first week, 101°F. for the second week with gradual subsidence. On the ninth day, a small hematoma about the lower

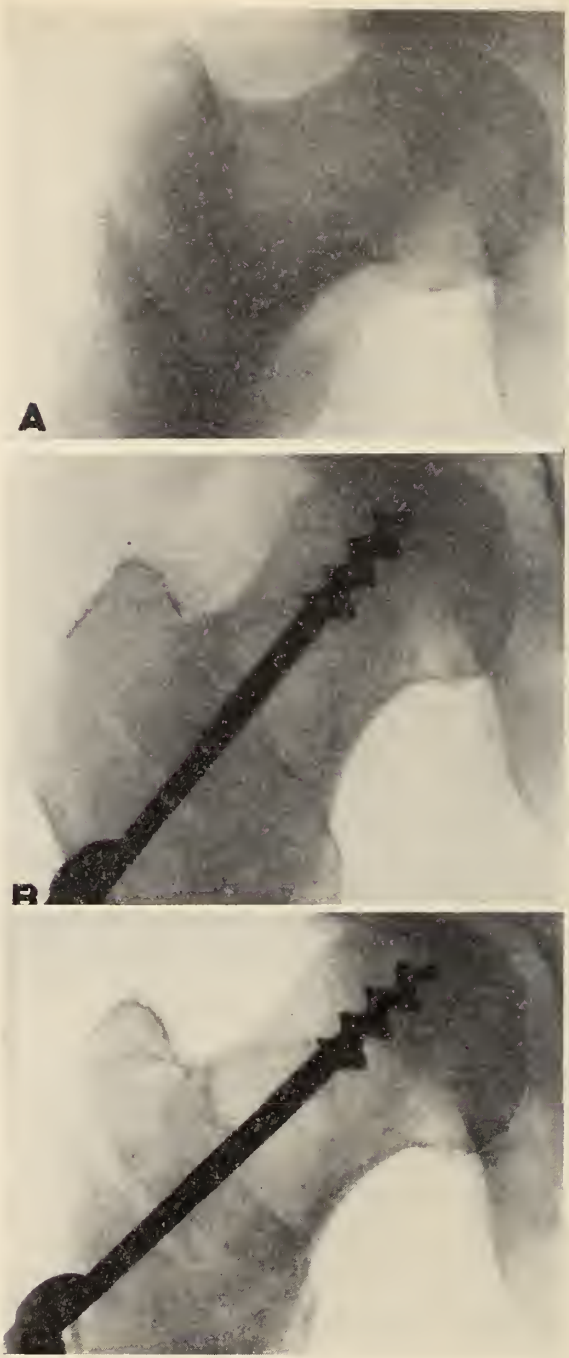

Fig. 1A. Case 1. Intertrochanteric fracture, February 5, 1939.
Fig. 1B. Postoperative roentgenogram.
Fig. 1C. Four months after operation.

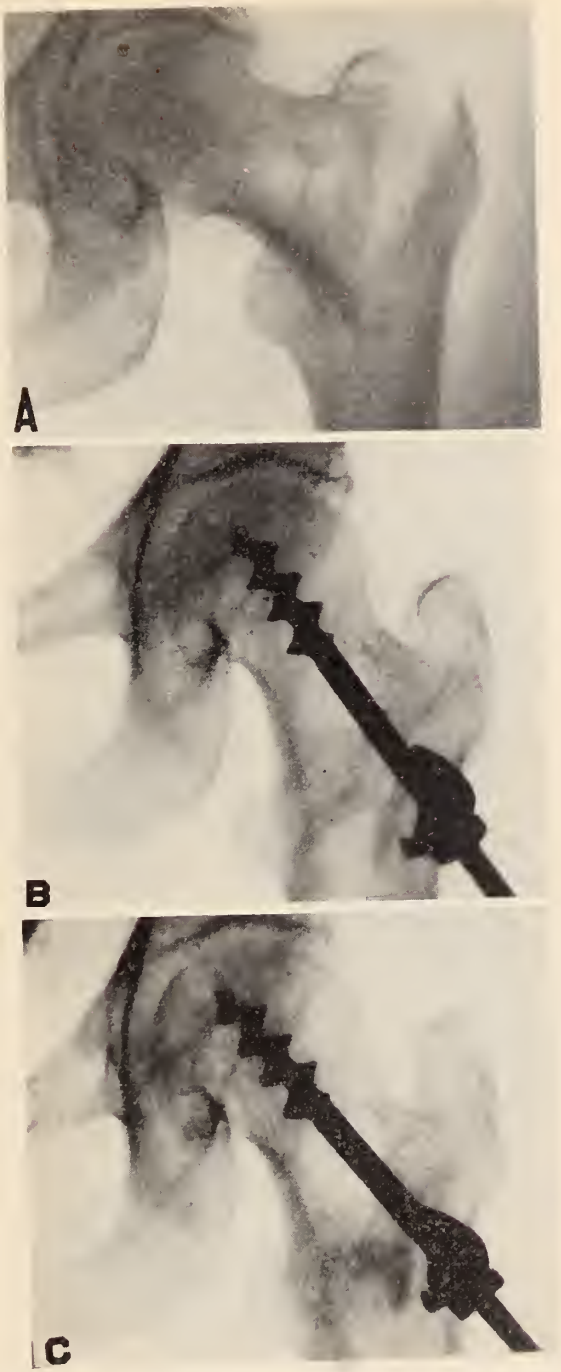

FIG. 2A. Case 2. Intertrochanteric fracture, January 1, 1940.
FIG. 2B. Postoperative roentgenogram.
FIG. 2C. Five months after operation.

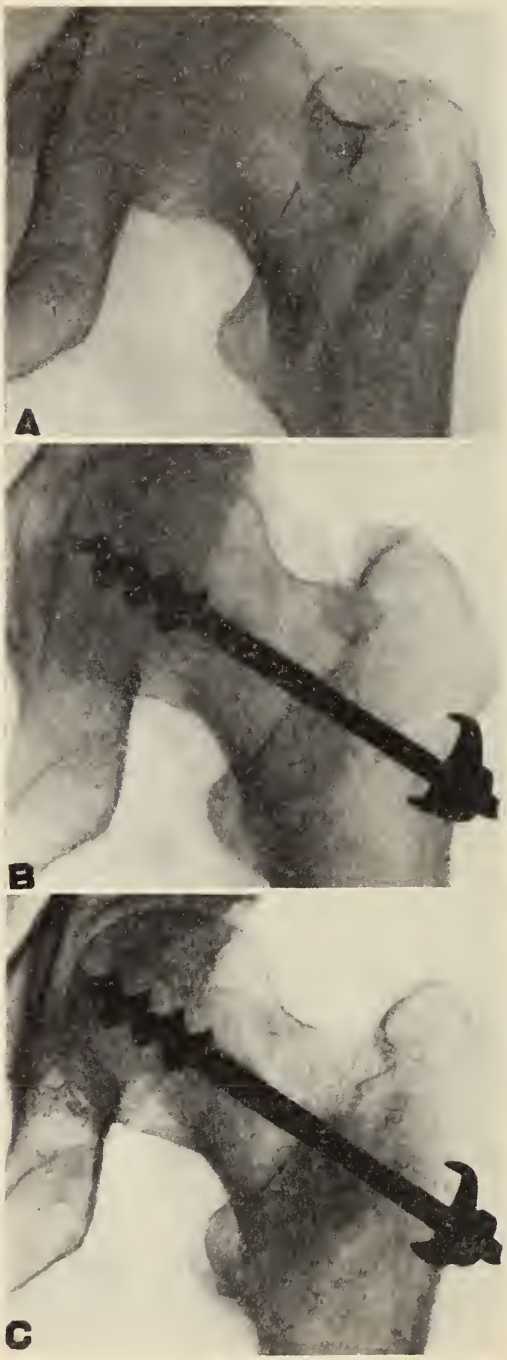

Fig. 3A. Case 3. Intertrochanteric fracture, March 13, 1940.
Fig. 3B. Postoperative roentgenogram.
Fig. 3C. Two months after operation.

angle of the wound was evacuated. The culture was sterile. One week after operation, X-ray examination showed complete maintenance of position (Fig. 2B). Recovery was slow but was otherwise uncomplicated. The patient was permitted to leave the hospital after the fourth week but did not begin walking on crutches for two and a half months. She was last seen on June 4, 1940 at which time she was able to walk without difficulty for a short distance. Her activity was restricted by dyspnoea due to circulatory failure, and by polyarthritic pain. Motion of the left hip was equal to that on the right side and there was no shortening. X-ray examinations five months after operation showed complete healing in excellent position (Fig. 2C).

Case 3. History. (Adm. 453774). H. A., a 64 year old woman, had a ten year history of severe arteriosclerosis and hypertension. A left hemiplegia following a stroke occurred one year ago with moderate residual spasticity but with fair leg function. She was admitted to The Mount Sinai Hospital March 15, 1940, two days after having fallen on the right hip. Clinical and X-ray examinations indicated an intertrochanteric fracture of the right hip (Fig. 3A). Shortening measured three-quarters of an inch. Internal fixation was performed five days later by Dr. A. Arkin and satisfactory position was obtained (Fig. 3B). One week after operation the patient was able to lift her heel from the bed. Convalescence was uneventful until the eighth day when the patient developed a chill, cough, and the temperature rose to 104°F. with signs indicating consolidation in the right chest. This was confirmed by X-ray examination and the blood culture was positive for pneumococcus type VIII. Sulfapyridine therapy was instituted and four days later the temperature was again normal and the patient asymptomatic. Seventeen days after operation, the patient was allowed to be up in a wheel chair and two weeks later, she began walking with the walking machine. Progress in walking was slow because of the spasticity of the uninjured leg. Two months after operation the patient was transferred to a convalescent home because of unsatisfactory home conditions. At this time she walked well with the aid of a crutch. There was no shortening or limitation of motion in the right hip joint which was entirely asymptomatic. Recent contact with the institution where the patient is now living reveals that her gait is now as good as before the occurrence of the fracture.

SUMMARY AND CONCLUSIONS

Statistics are in close agreement regarding the high mortality rate that characterizes intertrochanteric fractures and in the fact that the mortality rate increases rapidly with age. The cause of death in a large proportion of these cases is directly attributable to the complications of long immobilization. This data amply justifies attempts at internal fixation of these fractures in the elderly patient with the object of shortening the long bed rest period entailed by conservative therapy. On the other hand, there is no statistical justification for the internal fixation of trochanteric fractures in younger individuals who bear prolonged bed rest with impunity.

Because of its mechanical principle, as well as its ease of application, the corkscrew bolt appears to be a most suitable device for the fixation of intertrochanteric fractures. Use of the corkscrew bolt is illustrated by three case reports in which bed rest was markedly curtailed by internal fixation and excellent results obtained. A more comprehensive statistical

survey of intertrochanteric fractures treated with the corkscrew bolt at The Mount Sinai Hospital is deferred for subsequent publication.

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CHONDRO-SARCOMA OF THE RIB

Five Year Cure after Resection

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Although chondromata are considered to be benign lesions, they display a decided tendency to local recurrence after surgical removal. A malignant sarcomatous character is then to be noted occasionally. For this reason wide excision of a recurrent chondroma is indicated. A case of recurrent chondroma involving the chest wall seems to present a surgical problem of sufficient moment to warrant its report in this volume dedicated to a master of thoracic surgery.

CASE REPORT

History. Mrs. B. S., age 47, was first seen on April 20, 1935. Three years previously, a chondroma of the third rib had been removed by resection of the anterior portion of the involved rib. For two years the patient had been free of symptoms. She then noted the appearance of a lump in the chest wall near the situation of the original tumor and she began to experience recurrence of the same type of pain which had existed before the operation. The pain was not constant, and it was not very severe. The patient noted that pressure in the region of the tumor caused marked increase in the severity of the pain.

Examination. The patient was in good general condition. On the left side of the chest running parallel with the third rib was a five-inch scar just above which could be felt a rounded, firm swelling approximately two and a half inches in diameter. This was slightly tender to firm pressure. It was evidently firmly attached to the third rib. There was no enlargement of the axillary or supraclavicular lymph nodes. Further examination of the chest revealed no other abnormality.

Roentgenograms taken in January 1935 showed the presence of a definite tumor mass in the region of the third rib. Further radiographic studies (Fig. 1, 2) were made by Dr. Harry Wessler who reported the following: "The roentgen films show in the dorso-ventral position a faint shadow with indistinct outline which is situated at the level of the second to the fourth ribs anteriorly. On fluoroscopic examination of the patient and on the films taken in the oblique position, it is seen that this shadow corresponds to a well-defined mass, oval in shape and about two and a half inches in its vertical diameter, which extends outward from the resected end of the third rib on the left side. I believe that this mass is situated within the chest wall and that there is no connection with either the lungs or the pleura. I will not venture an opinion as to the exact nature of the mass except to say that on the roentgen film it appears to be sharply outlined and that it does not show any invasive character."

It was obvious that the patient was suffering from a recurrence of the chondroma and that a wide excision of the tumor mass was necessary. Since the tumor projected into the pleural cavity, it was also clear that the entire thickness of the chest wall, including the pleura, would have to be removed. The important problem in the

surgical technique was, therefore, the airtight closure of the pleural defect. Of the various methods which had been used it seemed to me that the implantation of fascia lata, as reported in two cases by Kirschner, was the simplest and most efficient.

Operation. The operation was performed at the Hospital for Joint Diseases on April 23, 1935, under avertin, gas and oxygen anesthesia. A seven-inch elliptical incision was made excising the scar of the previous operation. The tumor mass was then exposed by dissecting back the subcutaneous tissues and splitting the fibres of the pectoralis major muscle. It could then be seen that the tumor mass was approximately three and a half inches in diameter. It occupied the anterior portion of the third rib and impinged against the fourth rib. The area to be excised was then

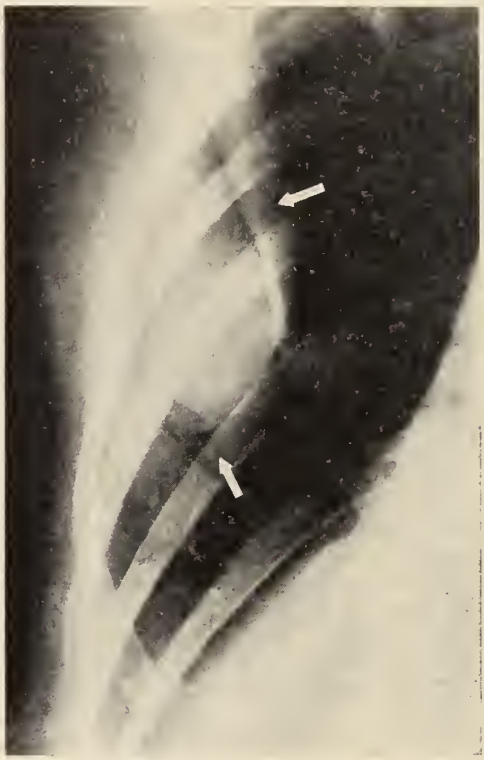

FIG. 1. Antero-posterior roentgenogram showing the tumor before operation

mapped out on the chest wall. It extended from the lower border of the second rib down to the upper border of the fifth rib, and from the sternum laterally for a distance of four inches. Through an incision over the lateral aspect of the left thigh, a strip of fascia lata was removed corresponding accurately in size to the area of the chest wall which was to be excised. A single fine chromic stitch was taken in each corner of the fascial graft. To prevent drying it was left *in situ* and the thigh incision temporarily closed with towel clamps. The excision of the chest wall was then done by first dividing the fourth rib close to the sternum, extending the incision through the thickness of the chest wall up to the second rib, then following its lower border for a distance of three and a half inches and, finally, running the incision downward to the fourth rib. The ribs were easily sectioned with the rib cutter. As the chest

was opened, the anesthetist increased the intra-pulmonary pressure sufficiently to prevent any collapse of the lung. The section of chest wall was then gently lifted away from the lung to which it was adherent by very delicate friable adhesions. As these were separated, a few bleeding points on the surface of the lung were caught and ligated. Because of the projection of the tumor into the pleural cavity, it had produced a slight indentation of the anterior surface of the lung. There was, however, no evidence of extension of the pathological process to the lung itself. The pleural surface covering the third and fourth ribs showed only a slight roughening due to the presence of adhesions. As rapidly as possible after removing the tumor mass, the fascial graft was sutured into position. This was done by taking a single

FIG. 2. Lateral roentgenogram showing the tumor before operation

suture at each one of the four corners of the incision. A continuous stitch was then made encircling the graft. This gave what seemed at the time to be an airtight closure. The subcutaneous tissues were then drawn together by plain catgut sutures, and the skin with a fine dermal stitch. The thigh incision was closed in similar fashion.

The pathological examination (Dr. H. Jaffe) showed "a tumor measuring 5 x 5 x 4 cm. It was composed of large mosaics of cartilage; in some places it was undergoing ossification. Sections showed a chondromatous tumor undergoing calcification and some ossification. In places the cartilage cells were accumulated in nests composed of rather immature small darkly-staining cells. These sections, compared with the original, showed progression of the growth in the direction of atypicalness and possibly malignancy. Changes like these are not infrequently encountered in chondromas".

"Diagnosis: Chondrosarcoma of rib, recurrence from a chondroma."

Postoperative Course. There was no change of the pulse after operation and no elevation of temperature subsequent to the operation above 100°F. for the first few days. The sole complaint was pain on respiration. Ten days subsequent to the operation, examination showed a moderate accumulation of fluid in the left chest. This was aspirated and 50 cc. of blood-tinged fluid removed. This was sterile on culture. The patient's highest temperature was 102°F. Although a little fluid reaccumulated following the aspiration, this had become completely absorbed by May 22, 1935, the date of her discharge from the hospital.

The further convalescence was uneventful except for one incident. Five weeks postoperatively a small swelling was noted near the inner portion of the wound. This was slightly sensitive and fluctuant. On aspiration there was a hissing noise evidencing the escape of a localized collection of gas. The tumor at once disappeared. A small pressure pad was applied and there was no further evidence of localized emphysema.

On follow-up to the present, there has been no evidence of any recurrence. The patient's general condition is excellent and she is free of all symptoms except difficulty in lying on the left side when sleeping.

X-ray examinations made five years and three months postoperatively show no roentgenographic evidence of recurrence. The resected anterior portions of the third and fourth ribs have not regenerated.

DISCUSSION

This case is reported first, as a five year cure following the removal of a recurrent osteochondroma of the rib which involved the entire chest wall and showed sarcomatous degeneration, and secondly, because of the interest attached to the operative technique. Heuer and Andrews in their article on "Tumors and Cysts of the Thoracic Wall" (Lewis's Practice of Surgery) write, "Sauerbruch states that in no other group of cases is the question of surgical pneumothorax of greater importance; and Hedblom is of the opinion that 'no surgical condition of the chest is more germane to the discussion of pneumothorax'; for the resection of the chest wall is usually extensive, and a large defect is produced in the absence of adhesions fixing the lung or stabilizing the mediastinum. Collapse of the lung may, therefore, be expected whenever the pleura is resected and symptoms, mild or serious, referable to the collapse of the lung may arise. Throughout the history of thoracic surgery the subject has been actively discussed and is still the subject of controversy."

In this case, collapse of the lung was prevented by the simple expedient of increasing the intra-pulmonary pressure with the gas-oxygen anesthesia apparatus. The airtight closure of the thoracic wound was accomplished with the use of fascia lata. Preparation of the fascia preparatory to the excision of the chest wall reduced to a minimum the period during which the pleural cavity was open and thus lessened the danger of air-borne infection of the pleural cavity. That the closure, though adequate, was not perfect was evidenced by the localized emphysema of the chest wall which developed five weeks postoperatively.

ON ETIOLOGY

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In discussions on etiology, the implications of the term "cause" have not always been fully grasped. The temptation is strong to visualize a cause as a single thing, a parasite or a poison for instance. A cause, however, may be contributory, primary or secondary, immediate or ultimate. The discovery of an inciting cause of a disease is an exciting event, but such a discovery represents merely the beginning of a parturition of a new chapter in science. In order to bring the child to full term, a host of contributory mechanisms must be uncovered, the invasive, immunological, pathogenetic, allergic, constitutional deficiency factors and so forth. For example, Laveran discovered the "cause" of malaria but it remained a sterile fact until Ross discovered the host in the mosquito. Hansen unquestionably discovered the "cause" of leprosy nearly sixty years ago, but the mechanism of invasion is still a mystery. Unfortunately, there are only a few diseases in which investigation has fairly completed the composite picture of etiology, so that our current lore concerning the cause of diseases represents mostly a series of variously developed embryos.

Disease is a dynamic and not a static process. The theory of relativity has its place in medicine as well as in physics. In other words, diseases have a biological range. Frequently the initial or larval phase differs from the terminal phase as the tadpole differs from the frog. Witness for instance the almost cataclysmic upheaval between essential hypertension and the end product, the cardio-vascular-renal syndrome of Bright's disease. Indeed, the different stages of a disease process have often acquired the dignity of separate and distinct entities, giving rise to the temptation to ascribe different etiologies, which is an obvious fallacy. A biological perspective of disease unifies instead of multiplying causality. The elucidation of the biology of disease is entirely the prerogative of the general practitioner, and not of the cloistered student in a laboratory. MacKenzie realized this over twenty-five years ago.

If disease is a biological process, there must be a mechanism. However, the cause of disease must not be confused with the mechanism whereby the disease like the embryo attains its fruition. The mechanism represents those altered functional processes induced by the inciting agent, or agents, that bring about morbid tissue changes. For instance, hyperthyroidism and the resulting changes in the thyroid gland are the dominant mechanisms of Graves' Syndrome, but the cause lies far behind these

mechanisms in point of time. Only too often the unraveling of the pathology and pathogenesis of a disease has resulted in the smug satisfaction that the "cause" of a disease has been clarified, but surely morbid anatomy is only an end result and only part of the total mechanism. To illustrate, the changes in the islands of Langerhans, discovered by Opie, undoubtedly represent the mechanism of glycosuria but these changes are surely not the "cause" of diabetes.

One wonders sometimes whether the distinction between cause and effect is not the most difficult accomplishment of human thought. The "dark ages" were dark because this accomplishment was clouded by dogma and tradition. Comets portended plagues, diseases were a dispensation of the Almighty, and Scrofula was cured by the King's touch. It was not ignorance but a lack of mental discipline that led to these distortions. When the shackles of dogma and tradition were loosened with the Renaissance, a burst of learning poured forth with the newly acquired freedom of thought. Bacon, Vesalius and Harvey created a vast impetus and for the first time medicine became a science. Before this medicine was mostly a shambles of distorted causes and effects. Both Vesalius and Harvey were great doubters. Indeed, they were among the first modern exemplars of this discipline of science. Even today, with a freedom of thought that Vesalius and Harvey would envy, this discipline is still regrettably not too deep or prevalent even among those who are trained in science. As a consequence, associated events and findings in disease are sometimes sadly mixed, and effects are regarded as causes, and vice versa. To illustrate, for decades arteriosclerosis was regarded as one of the main causes of hypertension. It remained for Mahomed, Huchard and Allbutt to show that the reverse was indeed the rule. Achlorhydria was once held to be the result of pernicious anemia. Thanks to Farber and to Hurst, we now know that it precedes by years the clinical evidences of pernicious anemia. A positive Wassermann reaction has led and still leads to innumerable errors in etiology when there is an associated disease that is not frankly syphilitic. For instance, the old text-books invariably mention syphilis as one of the causes of pernicious anemia. Ayerza made the same blunder in the syndrome which he described. The probability is strong that current medical lore is full of many of these distortions of cause and effect, and research on this topic alone is rich in opportunity.

This brings us to the time-honored problem as to what constitutes a disease. Much dialectic has been expended upon this problem. It seems to me that the most practical definition of a "disease" is this: a disease is a morbid process that has a consistent background in morbid anatomy. But pathology is not a closed science and there is hardly a disease in which the study of pathology or its genesis has been completed, so that for the present, we are forced to classify certain symptom complexes, syndromes and functional disturbances as diseases such as migraine, hyperchlorhydria

and hypertension, for example. A search for a unifying cause for these functional disturbances is set in motion and unless such is found we say that the "cause of the disease is unknown." In view of the integrated mechanism of function, it seems unreasonable to expect that a uniform factor is at fault and the chase is apt to lead to a mirage. It is just as reasonable to look for a uniform cause of headache.

The problem of etiology, therefore, must be concerned not with the discovery of a cause of a disease, but of the causes—of a how, and a when, and a why. In this sense, there is hardly a disease in which the complete etiology has been fully elaborated; and, on the other hand, there are few diseases in which at least part of the etiology is entirely unknown. Even in cancer, our knowledge of some of the contributory factors is considerable.

The statement, so fashionable in medical writings, that "the cause of a disease is unknown" represents almost always false humility. What is meant is that a vital link, or more likely several links, in the chain of circumstances are unknown.

One of the reasons why the discovery of these links eludes us is the tendency to think in terms of the past. We are only on the threshold of our knowledge of possible etiologies. Consider the number of new physical properties of matter that have been uncarthed within our memory such as light and heat and radioactivity; of new mechanisms, such as dietary deficiency, allergy, bacteriophage, the Shwartzman phenomenon; of new infecting agents, such as the Rickettsiae and the filterable viruses. Even our concept of life and matter is being undermined by the discovery of Stanley who showed that pure protein particles may act and grow as living things. This discovery of the cause of tobacco mosaic by Stanley may have far-reaching implications in the etiology of human disease. A cause that has received little sympathy until the last few years, but which furnishes vast opportunities for study, is the psyche. It is slowly dawning upon us that the impact of reiterated emotional influences upon a personality that is compounded largely of environmental and of genetic influences can actually cause organic disease. An evidence of the new faith is a journal devoted to the psychosomatic diseases. The genesis of these maladies subsumes the proposition that function may sometimes precede anatomy instead of reversely, a concept that would have been regarded as heresy twenty or more years ago.

In the light of this even incomplete array, it is just as probable that the discovery of new causes of diseases will come from a pure chemist, physicist or biologist as from one of our profession. Pasteur was not a physician, but had he not lived, the medicine of today would very likely be in a sorry state.

The summation of our argument is this: that in the study of etiology, more particularly than in almost any other chapter of medicine, the most important attribute of our thought, as in stroking the ball in tennis or in golf, is the "follow through."

TRANSURETHRAL RESECTION IN THE PRESENCE OF RENAL INSUFFICIENCY[1]

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A recent statistical survey (1) of the opinions of one hundred leading American urologists indicates the increasing popularity of transurethral prostatic resection. In this clinic, where two-stage suprapubic prostatectomy has been the method of choice for the relief of prostatic obstruction, transurethral resection is now performed in approximately 70 per cent of the cases. Preliminary drainage by urethral catheter and by suprapubic cystotomy has been very successful in reducing the mortality of suprapubic prostatectomy, particularly in the cases with renal impairment. Those patients in poor general condition or whose blood chemistry did not reach a sufficiently low level were often sent home for several months with suprapubic drainage to await more favorable conditions. Some of the patients with infected hydronephrotic kidneys had blood urea-nitrogen figures which never went below 50 or 60 mg. per 100 c.c. and hence seldom came to prostatectomy. This attitude of non-intervention was based on the very high mortality which followed prostatic enucleation in these cases.

Since the advent of transurethral resection, we have performed this procedure with surprisingly good results on a number of patients who had marked renal impairment. These cases were approached with great temerity and transurethral resection was usually performed only after persistent requests on the part of the patients. The dislike of, or intolerance to, the suprapubic tube were the usual motivating factors for these requests. The success of the procedure has offered new hopes for the self-neglected patient with prostatic obstruction who has tardily submitted to medical care after renal insufficiency is pronounced.

Because of our success in the patients with renal insufficiency it should not be assumed that the need for pre-operative care is lessened. However, Bumpus and Massey (2) believe that transurethral resection is a less dangerous procedure than prostatectomy and that the preliminary drainage required in order to do prostatectomy safely is not necessary for transurethral resection. Thompson (3) states that patients with uremia should be treated with an indwelling urethral catheter but if the blood

[1] Presented at the Monthly Urological Conference of The Mount Sinai Hospital, April 10, 1940.

urea is on the way down, it is better to proceed with the resection than to wait for complete subsidence of the azotemia. The same author (4) a year later writes that in the presence of renal insufficiency, continuous drainage by urethral catheter is employed until the concentration of urea in the blood has become stabilized at a level which assures that the operation can be safely undertaken.

It should be emphasized that the cases here presented are not those cases of renal insufficiency associated with acute episodes of pyelonephritis, such as are seen in the course of vesical neck obstruction. They are cases in which there is more or less permanent renal damage with impaired function. We believe that every opportunity should be given to improve renal function by drainage before considering prostatic resection. In other clinics suprapubic drainage would not have been performed in some of our cases. In this clinic, a small stab cystotomy is felt to be a procedure of great merit. It not only establishes more adequate drainage which tends to improve renal function but it acts as a safety valve by making the second stage transurethral resection much less hazardous. Thompson (5) has reported a brilliant result with transurethral resection in a patient who was admitted with a residual urine of 650 c.c. and a blood urea-nitrogen of 488 mg per 100 c.c. After indwelling urethral catheter drainage and intravenous supportive therapy, a transurethral resection was performed twenty-three days later when the blood urea concentration was 124 mg per 100 c.c. When the patient was discharged from the hospital the blood urea-nitrogen was 104 mg per 100 c.c. Although the result speaks for itself it is more than likely that we would have done a preliminary stab cystotomy in this instance.

Detailed herewith are some of the cases which were treated by transurethral resection in the presence of renal impairment.

CASE REPORTS

Case 1. History. (Adm. 440469.) B. R. R., a 57 year old Spaniard, was admitted to the Semi-Private Pavilion of the hospital on November 11, 1938. For ten years he had had urinary symptoms of difficulty in starting the stream, frequency, nocturia and dysuria. For the year before admission he had been catheterized daily. The residual urine varied between 18 and 32 ounces; it was extremely purulent. The patient was pale and obviously uremic. His blood urea-nitrogen was 87 mg. per 100 c.c. The phenolsulphonphthalein excretion was 0 per cent. The hemoglobin was 60 per cent; the blood pressure was 168 systolic and 94 diastolic. There was moderate prostatic enlargement, as determined by rectal examination, and a cystogram showed the bladder to be diverticulated. There was also some intravesical prostatic encroachment. Cystoscopy revealed middle-lobe enlargement and moderate lateral lobe enlargement. After indwelling urethral catheter drainage, the lowest blood urea-nitrogen obtained was 39 mg. per 100 c.c. but it immediately ascended to 64 mg. per 100 c.c. On November 28, 1938 a bilateral vasectomy and suprapubic cystotomy were performed under local anesthesia. The convalescence was uneventful except for occasional vomiting. The postoperative blood urea-nitrogen concentration was 78 mg. per 100 c.c. The patient was, therefore, sent home on

January 3, 1939 without further intervention. Under observation, his general condition improved greatly, but his blood urea-nitrogen never went below 60 mg. per 100 c.c. As a result of the patient's persistent demands, he was readmitted to the hospital on May 11, 1939 for transurethral resection. The resection was performed under spinal anaesthesia on May 20, 1939, six months after the suprapubic cystotomy. At this time his blood urea-nitrogen fluctuated between 60 and 70 mg. per 100 c.c. Twenty-seven grams of prostatic tissue were removed. The pathological report was "fibroadenoma." The postoperative course was absolutely uneventful until the fifth day when repeated vomiting began and lasted for five days. The vomiting was evidently an expression of marked renal insufficiency. He was treated with intravenous fluids and small doses of cocaine hydrochloride by mouth. The urethral catheter was removed on the fourth day and the suprapubic tube six days later. He was almost immediately dry suprapubically and voided adequately twelve ounces at a time. Because of a low hemoglobin the patient was given a blood transfusion of 500 c.c. He was discharged from the hospital on June 7, 1939 and has been well since. Although his urine is still purulent in spite of the administration of sulfanilamide and bladder irrigations, he now has no residual urine, he voids well, has gained in weight, and is very well pleased with his status. The blood urea-nitrogen concentration on April 11, 1940 was 29 mg. per 100 c.c.

Case 2. History. (Adm. 438190.) W. S., a 61 year old dentist, was admitted to the hospital on October 17, 1938. His symptoms were those of frequency, nocturia, and difficulty in voiding of three years duration. He refused medical treatment but finally, because of loss of weight and weakness, he consented to hospitalization. He appeared chronically ill, and had a residual urine of 32 ounces. The blood pressure was 180 systolic and 110 diastolic, and the hemoglobin was 73 per cent. The blood urea-nitrogen was 97 mg. per 100 c.c. The prostate was enlarged to about twice the normal size; it was firm and irregular, which was strongly suggestive of malignancy. Culture of the urine revealed B. proteus and Enterococcus. The cystogram showed a trabeculated bladder with intravesical prostatic intrusion. Inasmuch as an indwelling urethral catheter did not lower the blood urea-nitrogen concentration, bilateral vasectomy and suprapubic cystotomy for drainage were performed under local anesthesia. The postoperative course was stormy. The blood urea-nitrogen rose to 130 mg. per 100 c.c. and the carbon dioxide fell to 40.6 volumes per cent. Venoclysis with lactate Ringer solution was instituted and with an increase of the urinary output the blood urea-nitrogen fell to 63 mg. per 100 c.c. This was considered too high to permit further surgical intervention and the patient was, therefore, discharged on November 7, 1938 with the suprapubic tube in place. He remained under observation and repeated blood urea-nitrogen determinations were performed. The latter varied between 50 and 70 mg. per 100 c.c. Although his general condition improved somewhat, he suffered a great deal from vesical tenesmus and was readmitted to the hospital on March 30, 1939. Cystoscopy revealed marked middle lobe enlargement and moderate intravesical and intraurethral lateral lobe enlargement. On April 3, 1939, about six months after the drainage operation, a transurethral resection was performed with the removal of fourteen grams of prostatic tissue. An additional resection in the form of a revision was done on May 1, 1939 with the removal of three additional grams. The pathological report was "fibroadenoma." The postoperative course was uneventful. After removal of the suprapubic tube following the second resection there was prompt healing of the sinus. On discharge on May 6, 1939 the blood urea-nitrogen was 36 mg. per 100 c.c. The patient has gained weight and has improved remarkably. His urine is still cloudy with shreds. The last blood urea-nitrogen determination on January 20,

1940 was 42 mg. per 100 c.c., indicating persistent and probably permanent renal insufficiency.

Case 3. History. (Adm. 445310.) I. S., a 65 year old man, was admitted to the hospital on March 4, 1935. He had a history of vomiting, loss of weight and strength, constipation, and the development of a mass in the lower abdomen. Although at first the diagnosis was that of a carcinoma of the colon, it was later discovered that he had a prostatic obstruction, and that the "mass" was a distended bladder. The bladder was decompressed slowly with an indwelling urethral catheter and his blood urea-nitrogen fell from 85 to 35 mg. per 100 c.c. His blood pressure was 160 systolic and 80 diastolic; the hemoglobin was 50 per cent; and the phenolsulphonphthalein excretion was 0 per cent. A stab suprapubic cystotomy was then performed for better drainage. The blood urea-nitrogen fell to 31 mg. per 100 c.c. and it was decided to discharge the patient on April 14, 1935 until the blood urea level was sufficiently lowered to permit further radical relief of the prostatic obstruction. He was subsequently readmitted on several occasions with blood urea-nitrogen determinations which varied between 35 and 48 mg. per 100 c.c. Cystoscopy revealed a well-defined middle lobe prostatic enlargement with moderate intraurethral encroachment. Finally, he was readmitted on March 10, 1936 with his blood urea-nitrogen at the low level of 29 mg. per 100 c.c. and the phenolsulphonphthalein excretion at 20 per cent. Transurethral resection was performed, following which his blood urea-nitrogen rose to 64 mg. per 100 c.c. and the carbon dioxide fell to 20.5 volumes per cent. Supportive therapy brought these figures to more normal levels. Following removal of the suprapubic tube, persistent difficulty in voiding with a high residual urine made a second transurethral resection necessary. After this was performed the patient voided well, and the residual urine was reduced to four ounces. Pathological report of the resected tissue was "fibroadenoma." At the time of his discharge from the hospital the blood urea-nitrogen was 27 mg. per 100 c.c. The patient was observed in the Out-Patient Department and found to be comfortable. Three and a half years later, he was readmitted to the hospital with recurrent prostatic symptoms and a strangulated inguinal hernia which required operation. He recovered from the herniotomy but because of uremia with a large residual urine, a stab cystotomy had to be performed. After several days he finally died. Autopsy showed extreme bilateral hydro-ureter and hydronephrosis with bilateral chronic ureteritis and pyelonephritis. There were prostatic adenomata present with encroachment upon, and obstruction of, the prostatic urethra. The causes of death were renal failure and pneumonia.

Case 4. History. (Adm. 394581.) E. B., a 67 year old man, was admitted to the hospital on November 21, 1935. He had had symptoms of frequency, nocturia, and poor urinary stream with dribbling and slight incontinence for two years. His residual urine was sixteen ounces. The blood pressure was 196 systolic and 98 diastolic and the hemoglobin was 45 per cent. The phenolsulphonphthalein excretion was 9 per cent in four hours and the blood urea-nitrogen was 50 mg. per 100 c.c. By rectum, the prostate was felt to be about twice the normal size. Cystoscopy showed a diverticulated bladder with moderate median lobe and marked intraurethral lateral lobe encroachment. Bilateral vasectomy and suprapubic cystotomy were performed under local anesthesia on November 27, 1935. The drainage operation was done because there had been no response to urethral catheter drainage. Postoperatively the blood urea-nitrogen was 65 mg. per 100 c.c. and the patient was discharged from the hospital on December 12, 1935 without further intervention. He was observed for several months and the blood urea-nitrogen remained fixed at 27 mg. per 100 c.c. He was readmitted to the hospital on February 2, 1936. Under spinal anesthesia,

a transurethral resection was performed, eleven and a half grams of prostatic tissue being removed. The postoperative course was uneventful and he was discharged on February 16, 1936. Subsequently he had a persistent suprapubic fistula; this was closed by secondary suture and since then the patient has been well.

Case 5. History. (Adm. 426790.) H. S., a 65 year old man, was in the hospital from May to July 1938 suffering with bronchopneumonia. In addition, he had diabetes mellitus, coronary arteriosclerosis, chronic glomerulonephritis with contracted kidneys, renal acidosis, and prostatic hypertrophy. He was readmitted to the hospital on July 11, 1938. His symptoms were frequency, dysuria, and urgency. He had a residual urine of seven ounces. Examination revealed a thin, pale, old man with an enlarged heart and poor cardiac sounds. The prostate was moderately enlarged. The blood pressure was 150 systolic and 80 diastolic and the blood urea-nitrogen concentration was 58 mg. per 100 c.c. Cystoscopy showed intravesical and intraurethral lateral lobe enlargement. Bilateral vas ligation and transurethral resection were performed under spinal anesthesia. Five grams of prostatic tissue were removed. The patient made an uneventful recovery, voiding adequately at the time of discharge from the hospital, on July 28, 1938 but the blood urea-nitrogen was unchanged. The patient was seen in the Follow-Up-Clinic with blood urea-nitrogen figures varying between 48 and 88 mg. per 100 c.c., he was voiding well. However, he died at home five months later.

This case illustrates successful transurethral resection in the presence of chronic renal insufficiency probably only partially related to a prostatic obstruction. The renal insufficiency undoubtedly led to his death.

COMMENT

Most urologists agree that transurethral resection is a less shocking and less dangerous procedure than suprapubic prostatectomy. Today many poor risks who would previously have been untreated are being offered the benefits of this procedure. Prostatic patients with renal impairment who formerly had to lead a "catheter life" or carry a permanent suprapubic tube are being treated by resection. Our personal experience with this particular type of case has been very gratifying. Whether suprapubic cystotomy should be used before resection in the more severe cases of renal insufficiency is still a moot point. We feel, however, that cystotomy has added to the safety of the procedure in some of these patients.

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A NEW SOLUBLE VISCOUS CONTRAST MEDIUM FOR HYSTEROSALPINGOGRAPHY

Preliminary Report

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The first clinical injection of a radiopaque medium into the uterus was made in 1910 by Rindfleisch (1). Several years later the use of collargol for the same purpose was reported (Lelorier (2), Cary (3), Rubin (4)). Then followed the halogen salts (Rubin (5, 6), Kennedy (7) and others) which were displaced in 1922 and 1923 by the introduction of lipiodol and other iodized oils (Sicard and Forestier (8)).

The iodized oils enjoyed great popularity because they were better tolerated than their predecessors, giving at the same time excellent radiographic outlines of the uterine cavity and of the tubal lumina. The iodine proved to be capable of being taken up in great concentration by the poppy seed oil (lipiodol) and sesame oil (iodopine). The oil, moreover, had an advantage not generally recognized in that its greater viscosity enabled us to demonstrate permeable tubal strictures which was not possible with the use of aqueous solutions.

However, this advantage was offset by the disadvantage inherent in the oil, namely, the tendency to be trapped at tight points, giving rise, not infrequently to a foreign body reaction (9). Thus, an organic occlusion was induced artificially where some degree of patency was previously present. As strictured Fallopian tubes with some degree of permeability have been known to allow pregnancy to take place, the possibility of conception was thus prevented by the foreign body granuloma resulting from the retained lipiodol. Absorption and disappearance of the oil were in general much slower than of aqueous solutions and not infrequently the iodized oil was observed in the peritoneal cavity at laparotomy several years after its injection. More often opaque shadows were found by follow-up x-ray examinations several weeks and months after the oil injection. Particularly was this the case if the lipiodol was localized in peritubal, periovarian or general pelvic adhesions. In any event, although innocuous in most cases, the persistent presence of the iodized oil seemed to be undesirable. Among other things, the shadows may be confused with ureteral stone shadows as I have pointed out in previous communications.

Although the iodized oils marked a definite improvement over the radiopaque substances previously used, they did not fully realize the ideal

which was generally formulated as we gained more and more experience with hysterosalpingography.

The prerequisites of an ideal radiopaque substance to be employed for intrauterine injection (9, 10) are the following: 1) adequate radiopacity; 2) rapid absorbability; 3) freedom from chemical irritation; and 4) proper viscosity.

It is understood that the contrast medium must, in any event, be capable of being kept aseptic and possess bacteriostatic or bactericidal properties without injuring the tissues. The third prerequisite, freedom from irritation, is not so essential when the radiopaque substance is rapidly absorbed. The longer the solution persists in the tissues, the more likelihood there is of irritation. This has undoubtedly been the case with lipiodol, as the iodine which is organically combined with the oil does not permanently remain in the 40 per cent concentration but is liberated from its union with the oil and induces irritation by its persistent presence in the peritoneal cavity or within obstructed tubes.

During the last decade, crystalline iodine compounds in aqueous solution have been used, and have proven to be non-irritating, as they are tolerated by the blood stream when injected intravenously. Particularly is this true of the more modern radiographic crystalline iodine compounds employed in urology, such as diodrast and hippuran, and the most recently developed compound, rayopake.*

These substances are rapidly absorbed when injected into the veins for urographic purposes, being excreted in most instances during a period of 24 hours or less. They are also absorbed rapidly from the peritoneal cavity when injected into the uterus and through the Fallopian tubes, yielding kidney and ureter shadows if a sufficient amount has been introduced. In all respects, these crystalline iodine compounds satisfy the first three prerequisites. Being in aqueous solution, however, they pass through the uterus and Fallopian tubes so rapidly into the peritoneal cavity that, unless controlled by careful fluoroscopy, the diagnosis of one-sided or bilateral tubal patency can easily remain in doubt. Moreover, the spill into the pelvic cavity obscures the shadows of the tubal lumina if any solution still remains in them.

Several attempts have been made to overcome this disadvantage of the solutions of crystalline iodine compounds by adding a thickening substance. Neustaedter et al (10) suggested the use of 50 per cent glucose solution and I have experimented with stronger solutions which have a syrupy viscous character. They have proved irritating or non-feasible in the stronger concentrations and have other unfavorable features in the weaker solutions. Titus and his associates (11) recommended using acacia in 25 per cent

* Diethanolamine salt of 2,4-dioxo-3-iodo-6-methyl tetrahydropyridine acetic acid.

concentration, adding it to skiodan in strengths ordinarily used for intravenous urography. In work done on the monkey upon the comparative radiopaque substances used in uterosalpingography by Morse and Rubin (12), it was found that skiodan and acacia appeared to pass through the tubes as rapidly as aqueous skiodan itself.

The element of viscosity inherent in the iodized oils was not easily secured in non-oily media. The object of our research in this respect was to obtain a thickening substance of proved innocuousness which can be added to an aqueous solution of a crystalline iodine compound in appropriate concentration to render the latter viscous to a degree approaching that of lipiodol. In attacking this problem, the whole question of viscosity had to be considered, including the question, whether lipiodol had the ideal viscosity or whether a thinner oil might not be better, requiring less time for its absorption while not losing its desirable radioscopic and radiographic qualities.

In experimenting with a variety of thickening substances we finally found that a $3\frac{1}{2}$ per cent concentration of polyvinyl alcohol added to a solution of rayopake* has given results which appear to meet the ideal demands made upon it.

The viscosity of visco-rayopake as determined by a standard Saybolt viscometer, 60 cc. cup, at 98.5°F., was compared to the viscosity of water, skiodan with acacia and lipiodol. The results were as follows:

PREPARATION	SECONDS	APPROXIMATE RATIO
Water	30	1.0
Skiodan with Acacia	76	2.5
Lipiodol	1,657	55.2
Visco-Rayopake	3,720	124.0

In other words lipiodol is approximately 22 times and visco-rayopake 50 times as viscous as skiodan with acacia.

For the past year and a half we have had ample opportunity to test the substances leading up to the present development, both in animals and clinically. The toxicology was controlled by Dr. Theodore Koppanyi, Professor of Pharmacology at Georgetown University. His results are briefly summarized:

"The acute toxicity of the contrast substance (diethanolamine salt of 2, 4-dioxo-3-iodo-6-methyl tetrahydropyridine acetic acid) and the vehicle (polyvinyl alcohol) were determined by intravenous injections on rabbits and dogs. It was found that doses of 3 gms. per Kgm. weight of the contrast salt were well tolerated and that the average acute fatal dose was

* The solution of rayopake with the proper content of the viscosity agent was developed according to specifications by Hoffmann-La Roche, Inc.

4 gms. per Kgm. of body weight. In determining the acute toxicity of the polyvinyl alcohol, it was found that, due to the extreme viscosity of the material it was impossible to administer more than 2 grams of polyvinyl alcohol per kilogram of body weight (5 per cent solution, 40 cc. per Kgm.). These doses did not prove fatal to either rabbits or dogs.

"Chronic toxicity experiments were carried out by daily intraperitoneal injections into dogs, rabbits and rats over a thirty day period. At the end of this time the animals were killed and microscopic sections of the organs were made. The daily dose of the contrast salt varied with the different animals.

"The results obtained in these studies do not reveal any outstanding toxic action of these substances on the liver, kidney, spleen, adrenals, pancreas or gastro-intestinal tract. The few pathological changes which were observed could not be directly attributed to the substance injected. The kidneys of the albino rats which received large doses of the contrast media for over three weeks is the exception. Mild or severe renal irritation may be observed in this group. On the whole, it may be said that neither the contrast acid nor the polyvinyl alcohol produced, in moderate doses, either acute or chronic toxic effects.

"The compound when instilled for uterosalpingography is used in amounts ranging from 10 to 15 cc. The maximum amount of contrast acid given a patient is 8.25 gm. and the maximum amount of polyvinyl alcohol is 0.525 gm. Assuming that the average patient weighs as little as 50 kilograms, the amount of contrast acid a patient would receive by uterine instillation is 0.16 gms. per Kgm. and of the polyvinyl alcohol 0.01 gm. per Kgm. Recalling that an intravenous injection of 3 gms. per Kgm. of contrast acid and 2 gms. per Kgm. of polyvinyl alcohol is well tolerated, it is safe to conclude that patients tolerate the amount they absorb which is less than one fiftieth the maximum tolerated dose of contrast acid and less than one five hundredth the tolerated dose of polyvinyl alcohol."

Our work, done in the laboratory of The Mount Sinai Hospital fully corroborated Koppanyi's results, as far as the innocuousness of this new substance is concerned, when injected directly by abdominal puncture or through the uterus and oviducts into the peritoneal cavity of rabbits. In none of the animals were there gross signs of irritation, the abdominal cavity appearing normal after 24 to 72 hours. The abdominal viscera of the animals were inspected by laparotomy and the rabbits were used for reinjection or for other purposes later. None of the rabbits appeared to suffer any ill effects, continuing their fodder and activity as though they had undergone no experimental intervention.

Injection into and above the ligated portion of the uterus and oviducts of the rabbits resulted, as it usually does, in the retention of secretions which are poured out under such circumstances. It has been difficult to induce strictures in rabbits' oviducts in order to see whether the viscorayopake remains intercepted long enough to be filmed.

In its clinical application, the x-ray photographs of weaker concentrations of rayopake were completely satisfactory, and in its present concen-

FIG. 1. 3 cc. of visco-rayopake injected into the uterine cavity. Note defects and irregular contour of the cavity.

FIG. 2. 9 cc. of visco-rayopake injected into the uterine cavity. Many of the defects are obliterated. Note the dense shadow as compared to the speculum and pelvic bones.

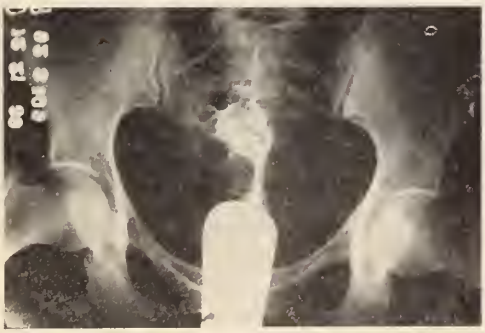

FIG. 3. Hystero-aerogram, 30 cc. of CO_2 used, showing the shadow defects as observed in Fig. 1 with the additional outline of the uterine cavity.

tration, 70 per cent, it naturally yields proportionately denser shadows. This becomes at once evident by comparison with the shadows of the metal vaginal speculum or of the bony pelvis (Figs. 1, 2, 3, 4, 5).

We have had occasion to use this new substance, visco-rayopake, in 81 cases. The quantity employed was in excess of that ordinarily used with lipiodol. The latter is scarcely ever injected in quantities greater than 10 cc. In the diagnosis of submucous myomata, for example, it was not uncommon to use 20 cc. or more of visco-rayopake. The pictures in all cases were satisfactory.

FIG. 4. Hystero-aerogram of extirpated uterus showing the multiple polypi and a well defined cavity outline.

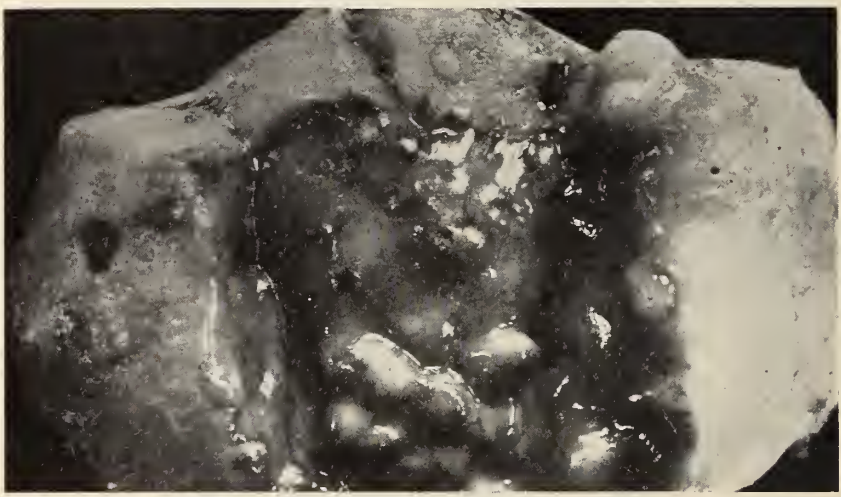

FIG. 5. Uterus opened showing multiple polypi and small submucous myoma.

It goes without saying that in all this work the careful consideration of clinical contraindications is of paramount importance. Untoward results may frequently be due to neglect of observing these precautions, although the contrast medium may be harmless. The only symptom which required evaluation was pain attending or following the injection. This symptom has generally not been appraised statistically in connection with other contrast media. In this respect visco-rayopake compares favorably with

lipiodol and the crystalline iodine solutions. An advantage over hippuran is the fact that it can be more conveniently handled in cold weather and gives better contrast pictures in fractional doses (Fig. 1).

In determining the clinical safety of this new substance, we took a risk in one patient when the injection was not favorable. A febrile reaction followed which required rest in bed for several days. The patient had had a plastic operation upon her Fallopian tubes with removal of extensive adhesions, twelve days before the injection. She recovered completely and retained the advantage of her restored tubal patency. From previous experience with lipiodol, it is fair to say that the reaction would have been at least as severe had the iodized oil been used under similar circumstances, while the retention of the oil could have induced foreign body reaction.

The visco-rayopake was put to more severe tests on some ward cases than would ordinarily come within its scope, because it was necessary to establish to what extend this substance may be used with or without harm. In ambulatory cases we have observed the strictest rules with regard to contraindications because the patients were not completely subject to constant observation. This precaution naturally holds for all methods of hysterosalpingography which permits the patient to go about instead of being confined to bed.

I have had occasion to use visco-rayopake in twenty-one office patients and the results have been satisfactory. The cases have for the most part been sterility cases, but in a number the diagnosis of submucous myoma was important. The scope of visco-rayopake is the same as that of lipiodol. Without entering into a discussion of the comprehensive value of hysterosalpingography in this preliminary report it may be said that the properties inherent in visco-rayopake give promise of enlarging the scope of hysterosalpingography, enabling us to resort to it for other purposes than the determination of tubal patency. It shares all the advantages of lipiodol and other iodized oils but appears so far to have none of their disadvantages.

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THORACOPLASTY IN CHILDREN

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As a tribute to Dr. Lilienthal, the pioneer in thoracic surgery, we dedicate this first study of Thoracoplasty in Children, carried out on the Pediatric Service of the Sea-View Hospital.

The study, covering a period of ten years, had its beginning at a time when even the simpler forms of surgery, such as pneumothorax and phrenicectomy, were considered as a radical departure from the then prevalent therapeutic routine of bed rest and good nutrition. Perhaps this conservative attitude may be explained by the frequent occurrence of the spontaneous resolution of a tuberculous process in the Childhood Type (first infection) of tuberculosis observed in children. The existence of destructive forms of the adult type of tuberculosis in children has been known, but these patients too, were treated in the same conservative way.

With greater experience it soon became obvious that the destructive type of tuberculosis in children with positive sputum and cavity formation in the lung, ran a course parallel to the similar disease in the adult. The adult patients were already receiving the benefits of the various types of surgical therapy, but the first pneumothorax in a child was given at Sea-View Hospital in the year 1928 and the first child had undergone a thoracoplasty in the year 1931.

In the ten years that followed, twenty-one young patients were operated on for thoracoplasty. This figure at first glance may appear to be small, but not when compared with the total number of patients receiving other forms of collapse therapy up to 1940.

Total number of patients receiving pneumothorax alone	123
Total number of patients receiving pneumothorax plus internal pneumolysis	40
Total number of patients receiving pneumothorax plus other surgery, e.g., thoracoscopy, phrenicectomy	15
Total	178

Thus, of 199 patients receiving some form of collapse therapy, 10 per cent had undergone thoracoplasty.

The early cases in which thoracoplasty was performed by our surgeons soon disclosed that the operation, although successful as far as controlling the tuberculous disease resulted in a complicating deforming kyphoscoliosis

with hindrance to growth, often more formidable than the disease itself. Consequently, the use of thoracoplasty for children was discouraged. Only those cases which were in the upper age levels and showed a more mature bony development, were selected for the operation. This factor played a considerable part in limiting the number of patients who were eligible for the operation.

The ages of the children on whom thoracoplasty was performed ranged between 8 to 16 years. There were 18 girls and 3 boys. This preponderance of female patients can be explained by the higher incidence of destructive forms of tuberculosis in the early adolescent female, and the corresponding increase in the female population on the service. Sixteen patients were white, and five were colored. The following table lists the age and sex grouping:

AGE AT TIME OF OPERATION	NO. OF CASES	
	Male	Female
years		
8	1	0
11	0	1
12	0	1
13	0	3
14	1	4
15	1	7
16	0	2

The patients chosen for operation were those in whom a pneumothorax could not be established, or in whom it was abandoned within a few months because of ineffective collapse.

Of these cases that were selected for operation, 7 (33⅓ per cent) out of the 21 cases revealed some evidences of tuberculous disease on the contralateral side.

In three of these seven cases with a contralateral lesion, attempts were made to control the lesion by pneumothorax on the unoperated side before the operation. In two patients, pneumothorax was maintained for a period of 8 months in one, and 2 years 8 months after the operation in the other. These patients are still in excellent condition, now three years after the operation. The third patient died during the operation.

The four patients with contralateral lesions who did not receive pneumothorax on the unoperated side, showed evidences only of an exudative productive type of tuberculosis with no cavity formation on the contralateral side. In one case there was progression of the contralateral lesion three years after the thoracoplasty.

There were four patients who developed a contralateral spread following thoracoplasty, where that lung previous to the operation showed no x-ray

evidence of tuberculous disease. The time of development of this spread was as follows:

PATIENT	DEVELOPED CONTRALATERAL LESION AFTER THORACOPLASTY OPERATION	FINAL OUTCOME
M. H.	3 weeks after 1st stage operation	Living—6 mos. after operation, good condition
M. V.	2½ years after operation	Living—4 years after operation, poor condition
F. M.	22 months after operation	Died—22 mos. after operation
S. M.	3 weeks after 1st stage operation	Died—16 days after 2nd stage of operation, wound infection

A number of the cases who were operated on for thoracoplasty had undergone additional surgical procedures either immediately before the thoracoplasty or at the time of the operation. They were as follows:

Spine fusion in 4 cases
Phrenicectomy in 6 cases
Internal pneumolysis in 2 cases
Apicolysis in 1 case

The spine fusion operation represents a notable advance in thoracic surgery in children. Its purpose is to prevent the deforming kyphoscoliosis that so often proved to be a menacing complication to the growth and appearance of the patient. The first operation of this type was performed at Sea View Hospital in 1936 and the patient is in excellent condition now, with no outward evidence of scoliosis.

The four patients who were subjected to spine fusion show the following results:

PATIENT	AGE AT OPERATION	YEAR OF OPERATION	PRESENT STATUS
	years		
A. H.	13	1936	Excellent
M. V.	11	1936	Poor—contralateral spread
D. J.	15	1937	Excellent for 1 year—present not known
J. M.	8	1938	Excellent

In the final analysis of the results obtained in these 21 patients who were operated on for thoracoplasty, 12 patients are known to be alive, 10 of these in excellent condition with a negative sputum and no clinical symptoms of tuberculosis. The time length of the follow-up is as follows:

FROM TIME OF OPERATION	LIVING PATIENTS
6 months	1
2–3 years	1
3–4 years	4
5–6 years	1
6–7 years	3
7–8 years	2
	DEATHS
At operation	2
16 days later	1
22 months	1
3 years, 5 months	1
3 years, 10 months	1
Unknown	1
Present status not known	2
Total cases	21

The present status of 2 patients in the series is not available although one of these patients was followed for a period of 5 years after the operation, with a persistently positive sputum. It is of interest that this patient had the benefit of pneumothorax, phrenicectomy, apicolysis and thoracoplasty with no sputum conversion at any time.

CONCLUSIONS

1. In destructive forms of lung tuberculosis in children, in which pneumothorax had failed, thoracoplasty holds a definite place as a means for surgical collapse.

2. Bilateral disease is not a contra-indication to the operation, provided the contralateral lung is controlled by some form of collapse therapy such as pneumothorax.

3. The spine fusion operation holds promise of diminishing the incidence and severity of the complicating kyphoscoliosis which has often occured in children as the result of thoracoplasty.

MEDICAL PROGRESS IN THE LAST HUNDRED YEARS

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During the past century, the mills of the gods have woven no other fabric so shot through, in both warp and woof, with the incomparably brilliant, gold and scarlet and royal purple as is the tapestry of medicine. Our difficulty lies not in conceding the wonders of accomplishment of the past century, but rather in setting down the facts on which they rest without ending up with a mere catalogue of assets. And if we are to escape the error of piling discovery on discovery and of glorifying discoverer after discoverer, then we must recognize in the first instance that, like man himself, medicine cannot thrive detached, but waxes and wanes in direct proportion to the inspirational impetus furnished her by the times in which she works. Eras, like men, have souls; but the perspective of time is required for their evaluation. With this thought in mind, one may unequivocally subscribe to the view expressed by Taine, the French historian and critic:

"On the eve of the nineteenth century the thinking public and the human mind had changed. A new world had arisen. The death of the guild system, the development of railroads, steamboats, textile machinery and the consequent birth of the industrial age led to the establishment of large urban centers holding hundreds of thousands of souls. Comfort, leisure, education and many of the other amenities that grace modern society became the heritages of the common man instead of the privileges of the chosen few. In the early eighteenth century, the total annual circulation of newspapers in England amounted to three thousand numbers—by contrast, long before one-half of the nineteenth century had passed, there were being distributed in England seventy-one million newspapers during the course of one year. The enfranchised and prosperous artisans assumed important rôles in governments, playing major parts in wars, commerce, inventions, science and politics. Careers opened up to talents. Under such stimuli, the human mind flowered and throughout the world there was as a consequence, a rebirth of manners, religions, philosophies and science."

What we choose to call modern man emerged during this nineteenth century of progress. The philosophy of democracy not only tinctured and colored, but it also dominated the minds of the men of this era, setting in motion currents and cross-currents that moved now slowly and now with

torrential force over established barriers and limits, finally coursing peacefully toward the delta of a transformation which we, in our day, can so clearly see by a mere glance over the shoulder.

How natural it was; indeed, how inevitable it was, that medicine of the nineteenth century should bear the impress of the stamp upon her of such epochal trail blazing as the theories of evolution proposed by Lamarck and Darwin, the atomic theory of Dalton, the law of the conservation of energy demonstrated by Mayer, the establishment of organic chemistry by Woehler's synthesis of urea and the annihilation of the doctrine of spontaneous generation by Pasteur. It requires little thought to grasp the idea that a century which, like the nineteenth, opened the doors for all talents should stimulate such intellectual activities as these. It requires even less effort of mind to appreciate the irresistible force of such a leaven after its transforming process of fermentation had once started.

The twentieth century contributes forty years toward the completion of the one hundred years that we are evaluating; and in general, estimating this short period as well as we can, handicapped as we are by its proximity and by our rôles as participants, it would seem that it has taken on the complexion of the preceding sixty years. There is, however, a notable variation. The nineteenth century represented a free course for all, with the the race to the swiftest. In the general meleé, speed and the mere idea of victory tended to crowd out all thought of how the race was run. In contrast with this spirit of *laissez-faire*, we are now, if for the moment we bar Germany, and Italy, engaged in the healthful process of moulding a finer social conscience. Garrison very succinctly summarizes the evidences of this tendency by recounting the efforts expended during the past third of the century on modern studies of foods, drugs, water, soil and sewage, the hygiene of industry and housing, the nutritional studies of children and adults, social surveys and settlement experiments, coöperative movements of various types, intensive studies of nation-wide prophylaxis against alcohol, gonorrhea, syphilis, tuberculosis and cancer; and finally the interlocking efforts of army, navy, institutes of science, universities and public health agencies of all sorts. This is neither the time nor place to hint at the explosive force of autocracy concealed within the folds of the fabric of fair ideals. There is little cause to fear that man will be sacrificed to the state unless man sinks to the pusillanimous level of meriting such degradation. This is the time and place, however to point out that just as the nineteenth century demonstrated the unshackling mechanism in the efforts of Darwin, Lamarck, Dalton, Mayer, Woehler and Pasteur, so likewise has the young twentieth century continued the demonstration in the stimulating and energizing influences of Bohr, Millikan, Compton, Einstein, Coolidge, Langmuir, Freud, Pearson, Ehrlich, Roentgen, Pavlov and Fischer, all of them fundamental scientists who lent color and direction to medical progress.

Such then having been the general drift of the last hundred years, part of which period lay in the nineteenth century, a smaller part in the twentieth it is now in order to set down the assets that have flowed to the account of medicine in the form of men, discoveries and procedures conserving health, life and limb, contributing to happiness and increasing the quantum of well-being throughout the world. And that sort of presentation holds within itself all the dangers and pitfalls inherent in literary strategy. Picture yourself comfortably thumbing through the pages of any adequate volume of medical history, noting merely the heroes who have come to constitute our gallery of Lares and Penates. Then assume the task of framing these household gods of medicine within the compass of a short essay! By what standard will you evaluate accomplishment so as correctly to group and classify the sowers, the reapers, the gleaners and the inevitable flock of geese who cackle over the discovery of an occasional grain of truth?

The surest way, it seems to me, is to concentrate on the larger conquests of the last hundred years of medicine rather than on the individuals responsible for victories. This means that it will suffice us, for example, to contemplate such a discovery as that of anesthesia as a gift of incomparable and incalculable beneficence without stressing the historic significance of Sir Humphry Davy, Crawford Williamson Long, William Thomas Morton, Charles T. Jackson, John Collins Warren, Horace Wells or Sir James Y. Simpson. It is significant that when the concept of "the death of pain" gripped the minds of men, there resulted, almost simultaneously, the discoveries of nitrous oxide, ether and chloroform anesthesia. And it is of no less interest that nearly half a century elapsed before the interacting brilliance of the minds of Sigmund Freud and Carl Koller furnished the world with the boon of local anesthesia, to be followed very shortly by spinal, sacral, intravenous and rectal anesthesia. In laying on the picture of this dramatic conquest of pain, as we must, in broad splashes with large brush, there should be no wasting of concern over the fact that there results inevitably a blurring of such vital details as the rôles played by Corning, Schleich, Matas, Halsted, Cushing, Crile, Gwathmey and the prohibitively long list of chemists and physiologists who contributed and are still contributing to the expanding field of painless surgery. The significant fact for us is that during the last hundred years the specter of surgical pain has been laid low.

Following a similar line of thought, even though we recognize that were prayers and paternosters, orisons and litanies to go up daily from every heart and hearth and pulpit throughout the world, in honor of Louis Pasteur, they could serve only as scant evidences of his service to humanity. And yet, with callous objectivity we stress only the fact that the last hundred years furnished the world with the means of combatting infection and thus conserving life and of converting hospitals from pest and

charnel houses of stench and blood and pain into havens of restoration, sweetness and light and life. Lord Lister's application of Pasteur's discoveries to clinical surgery and Semmelweis' and Holmes' anticipation of these same discoveries in the realm of obstetrics can claim from us only a reverent genuflection. The story that we are telling is that of gifts to humanity rather than of the agencies through which the gifts came, during the past one hundred years.

Pity 'tis that we can not even trace the fruits of the gifts as they ripened in the minds and through the efforts of surgeons. The last hundred years gave great surgeons to the world: Cooper, Syme, Liston, Brodie, Larry, Dupuytren, Velpeau, Malgaigne, Nelaton, Bigelow, Warren, Mott, McDowell, Sims, von Langenbeck and Simon, to select only a few from various lands; but these men spent their active surgical years before the introduction of antisepsis. After Pasteur was accepted came Billroth, Eiselsberg, Kocher, Trendelenburg, Tuffier, Chassaignac, Doyen, Jaboulay, Pozzi, Moynihan, Jones, Mayo-Robson, Makins, Bowlby, McBurney, Murphy, Bull, Weir, Senn, Fenger, Deaver, DaCosta and so on in every land and clime, shining in the light that their own times had furnished and, like the vestal virgins, tending that light in such a fashion as to preserve the blaze and heighten its brilliance.

No less brilliant have been the advances that have occurred in the non-surgical fields. Yellow fever disclosed the secret of her transmission to Reed, Carroll, Agramonte and Lazear. Once the secret was out, Gorgas saw to it that it was made public property. Typhoid fever similarly yielded to Eberth. The story is not much different in relation to plague, cholera, diphtheria, tetanus, scarlet fever, hydrophobia, epidemic meningitis and certain types of pneumonia. One has to shake oneself out of a dream, as it were, to grasp the reality of it all. But the facts are writ large in the founding of bacteriology by Koch, and the development of the new field by Roux, Behring, Loeffler, Klebs, Kitasato, Bordet, Welch, Smith, the Dicks, and who knows how many other workers in the fields of bacteriology, epidemiology and sanitation. With Schaudinn's discovery, and Noguchi's cultural studies of the spirochaeta pallida, there has come a better understanding of syphilis, and with Ehrlich's arsenic, a marked advance in treatment. The Peruvian romance of malaria was heightened when Laveran discovered the organism responsible for the disease and Ross located the mosquito as the carrier. All these victories rested on the orderly and logical procedure of reasoning from cause to effect. But even the failures to establish specific causes have not put insuperable barriers in the way, as may be witnessed by the partial conquest of diabetes, pernicious anemia, adrenal, thyroid, pituitary and gonadal hypo- and hyperfunction through the genius of Banting, Minot, Murphy, Swingle, Kendall, Doisy and Allen, Frank and countless others.

In internal medicine, just as we saw to be the case in surgery the adapters

of these fundamental discoveries, in other words, the clinicians, grew in accomplishment as the basic science of their specialty developed. When we contemplate what the pathfinders did for the oncomers when they established the principles underlying blood measurements by graphic instruments; blood staining and blood transfusion; the unraveling of the endocrine system; the mapping of the brain paths; the establishment of the various tests for functional activities; the visual inspection of the larynx, ear, eye, nose and the various hollow viscera; the rôle of bacteria and parasites in disease, the relationships between the physiology of heart and blood vessels and cardio-vascular diseases—when we contemplate just these few of the countless many brilliant activities of these pioneers the pathfinders, then it is not difficult to appreciate why the internists of the earlier of the past hundred years, solid and indispensable as they were, such men as Graves, Adams, Stokes, Cheyne, Bright, Hodgkin, Addison, Schoenlein, Wunderlich, Skoda, Nothnagel, Broussais, Louis and Bretonneau, clinical giants, all of them, were nevertheless of a different stripe from their colleagues, who came later and who could, therefore, lean so heavily on the newly acquired fundamentals. But here we tread on dangerous ground, for we are practically in our own day, speaking, literally, of ourselves. No stratagem of style and no assumed cloak of modesty could furnish satisfying assurance that what we say might not carry the false note of egotism. Perspective, perspective, always perspective is the keynote for the proper evaluation so necessary to the sound judgment of history.

Somewhere it has been said that no man can read all that has been written in any one limited specialty of medicine and retain his reason. With equal appropriateness may we say that reason reels in the attempt to coördinate, in detail, the progress in the field of medicine during the last hundred years; but since the attack has been made, the task must be completed by the enumeration of a few more of the solid building stones that the men of the past century have placed in the ever incomplete structure of medicine. Even such a seemingly simple selection is not an easy task, because it inevitably necessitates leaving out so many things that are important, even if they be not all keystones in the structural addition to medicine made during the past hundred years.

Virchow, laying the capstone on the labors of Johannes Mueller and Carl Rokitansky, published his "Cellular Pathology" in 1858, thus establishing the basis on which modern pathological thought and method rests, and incisively divorcing medicine from the complex humoralistic theories which had prevailed since the days of Hippocrates. Virchow's cellular concept necessarily rested on the studies of the botanist Schleiden and the anatomist Schwann, the discoverers of the cell as the unit in plant and animal structure—discoveries that were made during the hundred-year period that we are discussing.

It is more difficult accurately to date the birth of experimental physiology; but it would not be inaccurate to say that she too was the child of the century just closing. Purkinje in Bohemia, Magendie in France, Weber in Germany, Sharpey in England and Beaumont in America laid the ground-work, during the first half of this period, for the brilliant physiological studies that followed and that are still following.

Regarding embryology, we may be more accurate and place the birth date during the life of Carl Ernst von Baer, who, in the early days of poor microscopes and no microtomes, discovered the human ovum and cut wondrous microscopic sections out of which he constructed the ground-work for almost all that we know today of mammalian development. Likewise is it possible to give the exact date of the accouchement when medicine was delivered of radiology and radiotherapy. Roentgen and the Curies furnished the inseminating stimulus, considerably less than fifty years ago.

And then there is cancer! In truth still a house of mystery, in so far as specific cause or cure is concerned, but no less in truth a house several doors of which have been opened by keys of the experimental method, furnished in the first instance by Leo Loeb, in 1901, when he showed that cancer could be transplanted or grafted; in the second instance by Yamagiwa and Itchikawa, in 1914, when they showed that cancer could be produced, at will, by the use of tar; in the third instance by the countless investigators who have been busy for the past quarter of a century examining everything, animate or inanimate, in relation to cancer; and in the fourth instance by the clinicians, throughout the world, in their untiring labors with the problem of treatment.

And so we could continue with the story of the development or establishment, during the last hundred years, of such basic branches of medicine as public health, industrial hygiene, international hygiene, medical bibliography, pharmacology, biophysics, biochemistry and the purely technical advances, such as, among many others, micro-injection and micro-dissection techniques. We could elaborate further on what the last half a century has brought forth in the way of specialties such as orthopoedic and neurological surgery, genito-urinary and pulmonary surgery, otology, laryngology, ophthalmology and gynecology—that vast troop of not unmixed blessings that have at one and the same time furnished achievement, splendor and glory and tended to narrow the minds of practitioners within the bounds of specula, mirrors and small calibered tubes.

But we dare not continue, for our time has been set. There remains only a concluding note of caution lest we of to-day take unto our souls too much proud unction for all that which we may claim as the fruit of our own fertile brains. Nothing that the past hundred years has brought forth rests solely on its own bottom. Just as one cell inevitably must grow from a preceding one, just so is every newly discovered fact linked

in some way to the recent or remote past efforts of the medical heroes of the long ago.

All things by immortal power,
Near and far,
Hiddenly,
To each other linked are.
Thou canst not stir a flower
Without troubling of a star.

If it be true that there is no pride on earth like the pride of intellect and science, then it would seem that we may well be proud of our last century of medicine; but, in our pride, let us not forget Tennyson's quatrain:

Read my little fable;
He that runs may read.
Most can raise the flowers now,
For all have got the seed.

THE POSTERIOR MARGINAL FRAGMENT IN FRACTURES OF THE ANKLE

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In 1768 Percival Pott (1) wrote as follows, concerning fractures of the ankle: "But in its most simple state, unaccompanied by any wound, it is extremely troublesome to right, still more so to keep it in order, and unless managed with address and skill, is very frequently productive both of lameness and deformity ever after. If the bone be not kept in its place, the lameness and deformity are such as to be very fatiguing to the patient and to oblige him to wear a shoe with an iron or a laced buskin or something of that sort for a great while or perhaps for life."

Pott's fracture denotes the injury caused by eversion and abduction of the foot upon the leg. As the foot is everted, the stress is felt at the internal lateral ligament and the tibio-fibular ligament, and these are torn; or the internal lateral ligament may withstand the strain and the bone itself break transversely at the base of the internal malleolus. As the force continues, the fibula is fractured, usually obliquely at its thinnest portion several inches above its lower end. A not unusual complication of this injury is posterior displacement of the foot, usually with a fracture of the posterior articular margin of the tibia but occasionally without it. It is with this posterior marginal fracture of the tibia that this discussion will chiefly be concerned.

Any active orthopedic surgeon sees a surprisingly large number of painful, disabling ankles due to an unreduced posterior marginal tibial fracture. The lateral displacement with its consequent widening of the tibio-fibular mortise is usually recognized and effectively reduced and maintained, but the posterior displacement is sometimes overlooked. When one considers the voluminous literature on ankle fractures, surprisingly little has been written concerning the posterior marginal fragment of the tibia. Malgaigne, Tillaux, Hamilton, Dupuytren (2), Cooper, Cotton (3), Stimson (4), Dickson (5), Magnuson (6), Watson-Jones (7), Speed (8), Böhler (9), Hudson (10), Key (11), Scudder (12) and others have commented on the difficulties encountered in this injury. Cotton (3), in 1915, stated, "It is in fact one of the common and typical lesions of the ankle and its best claim to interest is because it is a lesion that everyone must have seen, interesting not from its rarity but from the very fact that it is common, that it is usually overlooked and that unless reduced, it results in serious disability in many instances."

Magnuson (6) stated, "If the fracture of the posterior lower end of the tibia is not completely reduced and held in reduction, serious disability results." He further stated, "If this manipulation does not bring the posterior lip of the tibia down into perfect apposition with the main body of the tibia, open operation should be done."

Watson-Jones (7) stresses the importance of the proper position of the astragalus and tibia but puts the emphasis on the relation between the astragalus and the articular surface of the tibia when he says "In the lateral radiograph it is the anterior portion of the tibial joint surface with which the astragalus must articulate. The position of the posterior marginal fragment is relatively unimportant. This fragment often remains displaced slightly upward and a step is formed at its junction with the main articular surface, but since the fragment is displaced away from the joint and not into it, this is unimportant. The functioning area of the articular surface may be slightly reduced, but the joint is stable, freely movable, and painless. On the other hand, if the astragalus is displaced backward, no matter how slightly, it articulates with the posterior marginal fragment, with a rough area of callus and with a sharp ridge; movement is limited and painful and osteoarthritis supervenes." In my opinion, however, this view that the position of the posterior marginal fragment is relatively unimportant is not valid. If the posterior marginal fragment is not reduced, there is usually a hiatus between the anterior portion of the articulating surfaces of the tibia and the fragment itself, and the astragalus has a tendency to gravitate into this hiatus. It is true, however, that if the posterior marginal fragment is extremely small, it may be ignored.

Böhler (9) states that after reduction of these fractures, they can only be maintained in good position by continuous traction or by fixation pins. Hudson (10) also advised the incorporation in the plaster of a fixation pin through the os calcis to maintain reduction. Pins may be necessary if the posterior marginal fragment is very large, comprising a third or more of the articular surface, but this procedure has not often been necessary in my experience. If the posterior marginal fragment can be completely reduced, it can usually be maintained by a properly applied plaster bandage, extending to the mid-thigh. If the reduction is only partial, however, the fragment has a strong tendency to displacement and the astragalus is prone to be displaced posteriorly into the articular defect. If manual reduction under satisfactory anesthesia is not possible, I have not found continued traction of much value in obtaining reduction. This also applies to the traction obtained by suspending the foot by means of a pin through the astragalus. In other words, during manual reduction under satisfactory anesthesia one can apply a maximal reducing effect, and if unsuccessful, one should not expect traction to reduce the fragments. The mechanics of the situation are entirely different from those

existing in a fracture of the long bones. It is wise, if manual reduction fails, to proceed with open operation and to maintain the posterior marginal fragment in position by means of a single vitallium screw.

The French surgeons (13, 14), stimulated by Dupuytren's excellent description of this fracture, have written more extensively on this topic.

The posterior marginal segment of the tibia is the posterior part of its lower articular surface and the backward sloping lower two inches of the posterior surface of the shaft, grooved by the tendons of the Flexor Longus Hallucis, and more internally, the Flexor Longus Digitorum and the Tibialis Posticus. The capsular ligament is attached to the posterior margin of the articular surface of the tibia. The articular surface rests on the astragalus, and it is that bone, by its displacement upward and backward, that causes the posterior marginal fracture. The posterior ligament of the ankle joint assists in producing the injury and the displacement. This fracture may occasionally occur without malleolar fractures by simple posterior displacement of the foot which happens, for example, when a runner stumbles forward with his foot in marked equinus. The posterior displacement of the foot may also occur without fracture of the posterior marginal portion of the tibia, the break taking place in the posterior tibio-tarsal ligament.

The clinical diagnosis is usually obvious in the more marked cases. If one compares the lateral appearance of the foot with the normal side, the exaggerated backward slope of the tendo Achilles and the prominence of the heel are almost pathognomonic. In cases with only slight displacement, a lateral roentgenogram often will disclose the first evidence of the injury.

I shall show the end-result of a case of unreduced posterior marginal fracture of the tibia.

Case 1. B. M., aged 47, an obese woman, fell on an icy pavement and suffered a fracture of the tibia and fibula (Fig. 1). In addition to the fracture of the internal malleolus and the fracture of the fibula, a triangular piece was broken off the posterior edge of the tibia and carried backward with the foot. An attempt at reduction was made under ether anesthesia. The post-reduction roentgenogram (Fig. 2) showed that improvement had been effected, but the reduction was not complete. Improvement is not sufficient in this type of fracture; an almost perfect anatomical replacement must be obtained if a good clinical result is to be expected. This patient, however, refused open operation and a second closed attempt at reduction failed to improve matters. She decided that the result would be good enough and refused surgery. She now has a disabling, painful ankle (Fig. 3).

The failure to reduce the displacement may have been due to interposition of the soft parts, either periosteum, or more likely capsule, or possibly a small bone fragment, as in the next case to be reviewed.

Case 2. (Adm. 385493.) E. Z., aged 16, male, a football player, suffered a posterior marginal fracture of the right tibia (Fig. 4) attached to a posteriorly displaced lower tibial epiphysis. This fracture occurred by direct backward displacement of the foot during a football game and was not caused by the eversion

mechanism of the Pott's fracture. In this connection Cotton has stated, "It has long been recognized that certain cases of so-called 'Pott's fracture' were complicated with a backward luxation of the foot. What has not been recognized is that nearly all of these cases are not really Pott's fractures at all." While I think

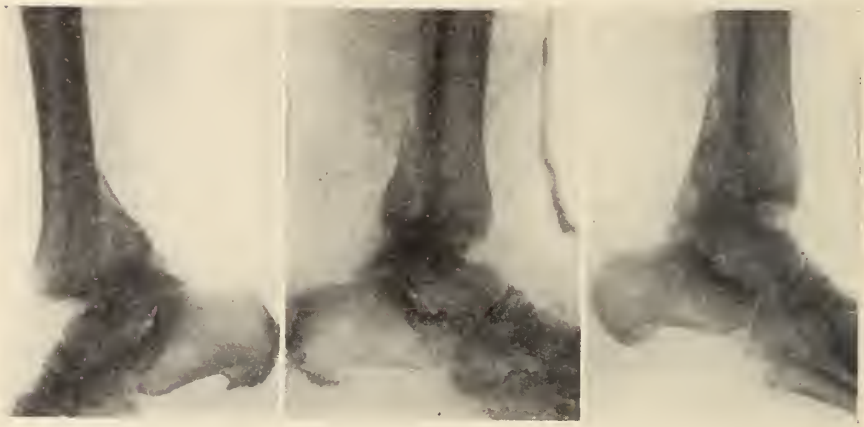

Fig. 1. Left. Case 1. Posterior marginal fracture of the tibia with typical backward displacement of the astragalus and foot.
Fig. 2. Center. Case 1. The fracture after reduction; unsatisfactory, even though the position is improved.
Fig. 3. Right. Case 1. Unsatisfactory end result in patient who refused open reduction.

Fig. 4. Left. Case 2. Posterior marginal fragment attached to the displaced epiphysis.
Fig. 5. Center. Case 2. Position after unsuccessful closed attempt at reduction.
Fig. 6. Right. Case 2. Excellent reduction after open operation and removal of interposed bone chip.

Cotton's statement is somewhat too inclusive, a certain number of the posterior displacements of the foot are not caused by the mechanism described by Pott.

On the antero-posterior and lateral views, a small fragment was seen interposed between the two main fragments. Closed reduction under ether anesthesia was attempted but proved unsuccessful (Fig. 5). Because of the presence of the intact epiphysis, the situation differed from that in Case 1. Even though the posterior displacement of the tibial fragment persisted, there was a normal articular surface.

However, if the displacement were uncorrected, excess callus formation at the anterior aspect of the articular surface of the tibia would interfere with normal motion at the ankle joint. A Kirschner wire was passed through the astragalus, as described by Dickson, and the foot was suspended by this wire in an attempt to reduce the fracture by traction, but the effort was unavailing. I assumed that we were dealing with the interposition of the small bone chip which could readily be seen in the x-ray film but can be visualized with difficulty in the prints that accompany this paper.

Through a four-inch posterior incision the tendo achilles was divided longitudinally and by blunt dissection through the muscle fibers of the Flexor Longus Hallucis, the fracture site was exposed. A periosteal elevator was inserted into the fracture, and the small bony chip interposed between the fragments was readily removed, and the fracture reduced (Fig. 6). No internal fixation was necessary to hold the fragments in place, because there was no tendeney to displacement when the foot was held in 90 degrees of flexion. A plaster bandage was applied from the toes to the mid-thigh with the knee flexed to a right angle to relax the gastrocnemius. After eight weeks the original plaster was removed and a walking plaster boot applied from the toes to the tibial tubercle. When this was removed at the end of three weeks the clinical result was excellent. Normal motion of the ankle joint was soon restored, with a minimum of physiotherapy. As a general rule the amount of physiotherapy after a fracture varies inversely with the excellence of the reduction.

COMMENT

I do not wish to give the impression that these cases are all difficult to reduce. Most of them can be readily reduced if the fracture is recognized and treated by the proper manipulation. However, correcting the lateral displacement of a Pott's fracture will not correct the posterior displacement. The maneuver to reduce the posterior displacement should be made under satisfactory anesthesia, either general or local, with the patient lying supine on the table, and the leg held down by an assistant. If no one is available, a loop made of strong bandage, reaching from the leg to the floor is kept under downward tension by the operator's foot. Traction on the tarsus is made in a distal direction by the operator who holds the foot firmly with both hands in about 25 degrees of equinus. While the traction is maintained, the surgeon gradually changes the direction of the force to a straight upward pull toward the ceiling, at the same time reducing the equinus until the foot is approximately at a right angle with the leg. If difficulty is encountered in reducing the fracture with this maneuver, it should be tried once more with the knee flexed to 90 degrees to relax the gastrocnemius. In addition, the associated malleolar fractures, if present, must also be reduced by the usual inversion maneuver. In applying the plaster, avoid extreme inversion of the foot. Only enough inversion should be used to maintain the proper position of the malleolei and the astragalus in its fork. If possible, the foot should be immobilized in the neutral position at an angle of about 90 degrees to the leg. The plaster should extend from the toes to the mid-thigh with the knee flexed at 90 degrees. If the surgeon is experienced in applying skin-tight plasters, this type should be used. If several days have elapsed

since the injury and the ankle is badly swollen, or if blebs are present, the extremity should be immobilized for several days by means of a wire through the os calcis until the edema has subsided.

The original plaster should be changed in four or five weeks to a snugly fitting walking plaster, extending only to the tibial tubercle. The time to change the plaster varies with the severity of the fracture. It is possible to lose position even after one month, and if a tendency to displacement was noted at the time of reduction, the change of plaster can be postponed for as long as six weeks after the injury. The walking plaster should be continued for four or six weeks after that. I have seen little residual stiffness of the ankle or tarsal joints due to long plaster immobilization if the fracture had been properly reduced and if the patient walks in the plaster boot.

After removal of the plaster, a gelatin bandage or a firm adhesive dressing should be applied from the toes to the tibial tubercle to control the edema. If adhesive is used, it should be applied over a bandage, rather than directly to the skin. Very little physiotherapy will be needed before motion is essentially normal at the ankle joint. If the reduction has been unsatisfactory, however, the patient will have to be treated by physiotherapy for an indefinite length of time. In spite of persistent treatment, a painful traumatic arthritis will develop at the joint between the astragalus and the tibia, and ankle fusion will probably become necessary.

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PRINCIPLES OF TREATMENT IN PERIPHERAL VASCULAR DISEASE

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A knowledge of the physiology of the peripheral circulation is a necessary basis for the intelligent treatment of patients who suffer from peripheral vascular disease. To meet varying needs, the circulation in normal extremities is increased or diminished. Furthermore, changes in blood flow may be selective, so that an increase may take place in the muscles while a decrease occurs in the skin, and vice-versa. Many forms of treatment now employed unconsciously utilize such normal physiological reactions, and in many instances two or more methods used simultaneously merely duplicate each other by employing the same mechanism. To clarify these points, the conditions which produce alterations in the normal peripheral circulation will first be described. Certain complicating factors which arise from the presence of arterial obstruction will then be briefly discussed. Finally, some of the methods now employed in treating patients with thrombo-angiitis obliterans and arteriosclerosis will be analyzed to determine the principle underlying each form of treatment, and to group together the forms utilizing the same mechanism. Discussion of the treatment of vasospastic conditions, such as Raynaud's disease, will not be included in this paper.

The functions of the circulation in the extremities are: To aid in regulation of the body temperature; to supply nutrition to all the tissues under varying conditions; to combat infection and inflammation.

The following eight physiological principles are the reasons underlying our attempts to increase the circulation in the extremities.

1. The ability to vary the volume of circulation in the extremities constitutes one of the important means for regulating the body temperature. The skin of the terminal portions of the extremities is richly supplied with curious neuromuscular arteriovenous anastomoses regulated by the sympathetic nervous system. When these canals are opened, a veritable flood of blood passes from the arterial to the venous channels. In addition, vasoconstriction and vasodilatation of the arterioles allows wide variations in the amount of blood flow. The internal body temperature remains relatively constant in spite of wide fluctuations in environmental temperature. On the other hand, the surface temperature of the fingers and toes varies tremendously, and may change from 70°F. in a cold room to 95°F. in a hot room. These wide variations in the surface temperatures of the

digits are to a great extent produced by changes in the volume of blood flow in the extremities. To maintain body temperature in a cold environment the circulation in the extremities is reduced to prevent heat loss, and in a hot environment, the peripheral circulation is increased to aid heat loss.

Regulation of the circulation in the extremities for the purpose of maintaining an even systemic temperature is accomplished by the activity of the sympathetic nervous system. In the skin, sympathetic stimulation causes vasoconstriction, while inhibition of sympathetic activity permits vasodilatation. In the calf muscles, sympathetic stimulation produces vasodilatation, and inhibition of sympathetic activity is followed by slight vasoconstriction. (1, 2).

Vasodilatation may be produced by increasing the environmental or internal temperature of the body. Gibbon and Landis (3) have described a test which depends on this reaction. When both upper extremities are placed in a water bath maintained at a temperature of 45°C., the surface temperature of the toes will be raised to approximately 35°C. (95°F). The warmer blood returning from the heated upper extremities stimulates the central heat-regulating center in the brain. This results in vasodilatation due to inhibition of sympathetic activity in the lower extremities (4). Simultaneous determinations of the muscle temperature by thermocouple needles inserted in the calves show no rise, indicating that such reflex vasodilatation is confined to the skin (1). Plethysmographic studies by various investigators show a marked increase in blood flow in the extremities in response to this test (2, 5, 32).

Any method producing paralysis of the sympathetic fibres to the lower extremities likewise results in a striking increase in the skin surface temperature of the feet due to vasodilatation (7). Simultaneous determinations of calf muscle temperatures show no corresponding rise. Such changes have been observed after both paravertebral injections of alcohol and spinal subarachnoid injections of novocaine (1).

The essence of the above discussion may be condensed into the first physiological principle as follows: *The circulation in the extremities may be greatly increased by vasodilatation in response to inhibition or paralysis of sympathetic activity in the extremities. Such vasodilatation occurs in the skin, but not in the muscles.*

2. The blood flow to a normal resting extremity at a comfortable temperature is at a low level. An extraordinary increase in circulation can be produced by applying heat directly to the hands or feet. Plethysmographic studies by Grant and Pearson (2), Freeman (5), Abramson and Zazeela (6), and Wright and Phelps (32) are all in agreement on this point. The average resting blood flow in a normal lower extremity at 32°C. is about 4 c.c. per 100 c.c. of foot volume per minute. When the temperature is raised to 45°C., the average reading becomes about 16 c.c.,

a 400 per cent increase. An elevation in the temperature of cells causes an acceleration of metabolism (8). The striking augmentation of circulation which occurs when the environmental temperature of the foot is raised is a response to the increased metabolic needs of the tissues (5).

Conversely, when the extremity is cooled, the metabolic needs of the tissues are progressively diminished, and a corresponding decrease of circulation follows. Plethysmographic studies show that reducing the environmental temperature of the feet from 35°C. to 25°C. results in reducing the blood flow to 25 per cent of its previous figure (5, 9).

The second physiological principle established, therefore, is that *the circulation in the extremities can be varied by increasing or diminishing the metabolic needs of the tissues which result from directly heating or cooling the hands or feet.*

3. The blood flow to the resting *muscles* of a normal extremity is likewise at a low level. A marked increase in the circulation to the muscles results from exercise, and the hyperemia produced is proportional to the duration and vigor of the muscular effort. This has been shown by both plethysmographic studies (10) and by measuring the temperature of the muscles (11). During exercise the surface temperature of the skin of the extremity falls, but subsequently it rises far above the initial level (11).

To meet conditions of stress, where combat or flight are required to preserve the life of an animal, the circulation of the muscles would naturally need to be increased. Under such conditions it has been shown by Cannon (12) that an increased amount of adrenaline is poured into the blood stream. Numerous investigators have shown, both in animal experiments and in studies of the human extremities, that intravenous injections of adrenaline produce a striking increase in muscle circulation (1, 12, 13). The third physiological principle may be stated as follows: *the circulation to the muscles of the extremities is increased by exercise and by conditions of stress associated with the liberation of adrenaline into the blood stream.*

4. It is known that the blood supply to an extremity may be completely shut off with a tourniquet for a considerable period without danger. However, when the tourniquet is removed, a blood flow much greater than normal develops in the extremity (14). This reactive hyperemia persists until the "blood debt" to the tissues has been repaid (5). Similar reactions of lesser degree follow partial occlusions of the circulation. Simpler manifestations of the same phenomenon are readily observed in the skin. Pressure against a portion of the skin overlying a bony point deprives this area of its normal nutrition. When such pressure ceases, the marked redness which develops is evidence of reactive hyperemia. Although considerable study has been devoted to this reaction, the mechanism underlying it is not clearly understood. It is probable that lactic acid accumulates while the circulation is arrested. If the tissues are deprived of blood for a longer time, a histamine-like substance is also formed. Both

of these chemical substances are able to produce vasodilatation (5). In any case, a sharp increase in limb circulation results when the blood flow is restored. It may therefore be stated as a fourth physiological principle that *reactive hyperemia develops whenever the circulation to a part has been totally or partially arrested for a limited time.*

5. It is a matter of common observation that any inflammatory process in the skin presents evidence of an increase in the local circulation. The local heat and redness are evidence of such hyperemia. Simple examples are the inflammations which result from insect bites (mosquito bites, bee stings, etc.). Local skin infections (furuncles, cellulitis) also produce similar reactions. It is apparent that the more extensive the inflammatory reaction, the more pronounced will be the increased circulation to the part. All surgeons recognize and expect to find a greatly increased vascularity in any tissues which show active inflammation. The fifth physiological principle may therefore be briefly stated as follows: *An increased circulation to the extremity occurs in response to inflammation.*

The foregoing discussion permits us to visualize the mechanisms which are employed in a *normal* extremity to increase the circulation. Before proceeding to an analysis of methods of treatment employed in patients with peripheral vascular disease, it is necessary to consider briefly in what manner the presence of obstruction of the peripheral arteries complicates the problem.

6. In a normal extremity the peripheral vessels are kept in a state of constant vasoconstriction of greater or lesser degree in order to aid in regulating systemic temperature. The individual who has peripheral vascular disease likewise must maintain an evenly regulated systemic temperature. It is not surprising, therefore, to discover that in extremities in which the circulation is impaired by peripheral vascular disease, a considerable and varying degree of vasoconstriction persists. Such vasoconstriction must be regarded as physiological, and it is improper to refer to it as "spasm", which implies a pathological state (15). This term should be reserved for true instances of intense arterial constriction of relatively short duration, such as those produced by cold in Raynaud's disease or by trauma to the arterial wall. In other words, the circulation in the extremities is diminished by two factors, one being the reduction or occlusion of the lumen of major arteries by the disease process, the other being the superimposed vasoconstriction maintained for the physiological needs of the body as a whole. It is necessary to keep in mind which one of these components is being affected by the method of treatment employed. The sixth principle may be stated as follows: *Physiological vasoconstriction persists in an extremity in which the blood flow has been reduced by peripheral vascular disease. Such vasoconstriction is not "spasm".*

7. The following consideration is also of importance. When a major artery is occluded, the blood flow is carried around the point of obstruction

by accessory channels, which we call the collateral circulation. In response to need, such channels may greatly increase in size, and ultimately may serve as a very satisfactory substitute for the original arteries. However, the increase in collateral circulation may require a considerable time. One object of treatment is to hasten the development of such accessory channels and to increase their size so that a greater amount of blood can be transported through them. Any method of treatment which could be shown to have this effect would have great value.

It is important to distinguish clearly between *vasodilatation* and *collateral circulation.* The former term applies to the sudden widening of already existing channels, the latter to the slow development of new channels. For example, immediately after an embolic occlusion of a femoral artery the circulation to the extremity is seriously impaired. A spinal anesthesia will cause complete vasodilatation and thereby increase blood flow to the extremity through all available existing arteries. If the circulation has been reduced to 5 per cent of normal by the embolism, complete vasodilatation by this means may increase it to 10 per cent of normal. However, in the course of a few weeks, new channels will develop and the circulation may be increased to 20 per cent of normal or more. The latter increase represents the improvement in circulation due to development of collateral circulation. The seventh principle, may be expressed as follows: *Considerable time is required for the development of new channels to carry the blood around a point of arterial obstruction. This process differs from vasodilatation.*

8. Finally, venous occlusion as a principle of treatment in patients with arterial obstruction must be briefly discussed. During the World War it was accidentally discovered that the incidence of gangrene following ligation of a damaged major artery could be greatly reduced if the companion vein were deliberately ligated at the same time (22). Numerous animal experiments by Brooks (16), Holman (17), and others confirmed this observation. The principle involved may be briefly stated as follows: Although ligation of the companion vein after arterial occlusion still further diminishes the flow of blood through the limb, it has a beneficial effect because it increases intravascular pressure in the extremity (25). Such an increased tension restores an adequate filtration pressure in the capillaries and aids in maintaining the nutrition of the cells. It is obvious that this principle is applicable not only to the treatment of acute arterial occlusion, but to chronic forms of obstruction as well. The last principle is that *when arterial inflow is seriously reduced in an extremity, intravascular pressure can be maintained if venous outflow is correspondingly reduced.*

Having stated the principles which underlie our attempts to increase the circulation in the extremities, we are now ready to scrutinize the methods of treatment which have been proposed, and to group together those which appear to depend upon the same mechanism. Pending more

certain knowledge, some methods must be tentatively included in groups where they may not belong. The chief forms of treatment may be listed as those which increase circulation in the extremities by: (a) reflex vasodilatation; (b) paralytic vasodilatation; (c) increasing local metabolism; (d) vasodilatation by drugs which relax smooth muscle; (e) venous occlusion and reactive hyperemia; (f) inflammation; (g) exercise; (h) intravenous injections of hypertonic solutions.

a. Reflex Vasodilatation. The circulation in the extremities is increased by reflex vasodilatation whenever the maintainance of the normal body temperature is threatened by an increased environmental temperature. This is equally true whether the individual goes to a hot climate, enters the steam-room of a Turkish bath, or takes a hot bath at home. It is likewise true, but to a lesser degree, when heat is applied only to a part of the body by hot water bags, electric pads, or a baking apparatus. When the entire body is wrapped in heavy blankets, a similar reaction develops, due to the fact that there is interference with normal heat loss. Antipyretic drugs, such as aspirin, promote heat loss by increasing peripheral vasodilatation. Effective vasodilatation may be assumed to be present when the individual perspires.

When fever is produced by the intravenous injection of typhoid vaccine or any other foreign protein, heat loss is increased by opening up the peripheral blood vessels. As a method of producing this reaction, fever is no more effective then the use of some form of externally applied physically induced heat. On the other hand, the initial chill produced by an injection of typhoid vaccine is undesirable, as it predisposes to thrombosis.

As previously indicated, *reflex vasodilatation* takes place only in the skin and not in the muscles (1, 30). It is therefore of value in the healing of ulcers of the skin, but cannot be expected to benefit intermittent claudication, which is due to insufficient circulation in the muscles.

Since smoking increases vasoconstriction in the extremities, the continued use of tobacco may defeat efforts to produce vasodilatation by any therapeutic measures. Therefore in all forms of peripheral vascular disease the use of tobacco in any manner should be forbidden.

b. Paralytic Vasodilatation. When the activity of the sympathetic nervous system in the extremities is diminished or abolished, the arterioles and arteriovenous anastamoses are permitted to dilate, and a marked increase in blood flow to the skin results. Such a diminution of sympathetic activity results from any form of anesthesia (general, spinal or local) but it may also be induced by sedatives. All sedatives lessen the activity of nerve cells and are therefore closely related to the drugs which produce anesthesia. Alcohol is known to have a similar effect.

More direct attempts have been made to abolish sympathetic activity in the extremities by operative procedures. Leriche first attempted this by removing the adventitia of the larger arteries which contain the sym-

pathetic fibres. For anatomical reasons, this operation was ineffective and has been discarded. Sympathetic ganglionectomy is now recognized as the most satisfactory method of producing paralytic vasodilatation in the vessels of the extremities. Paravertebral injections of alcohol, while a less satisfactory method, accomplish the same object. The removal of one adrenal, an operation which gained favor in Europe for a certain length of time, probably owed whatever effectiveness it had to the diminished sympathetic activity which resulted from lessened adrenaline secretion. The latest operation recommended is arteriectomy of occluded major arteries (26). It is claimed that the occluded artery sets up reflex disturbances which result in vasoconstriction. Without going into the relative merits of these various procedures, it should be clear that by each one sympathetic activity is lessened or abolished, and it is by this mechanism alone that the circulation is increased.

Sympathetic ganglionectomy is undoubtedly the most effective of the methods mentioned. It produces permanent but not maximum vasodilatation, and effectively increases the circulation in the skin for twenty-four hours. This aids in the healing of ulceration, and probably helps to prevent recurrent ulceration. These results may be accomplished by non-operative means. The operation has a definite mortality; it may be followed by impotence, bladder or bowel disturbances; it is ineffective in advanced cases of peripheral vascular disease; it interferes with the normal heat regulation of the body, and it fails to relieve intermittent claudication, because it does not result in an increased circulation in the muscles. For these reasons, it should not be recommended too hastily for patients with thrombo-angiitis obliterans or arteriosclerotic peripheral vascular disease.

c. Increasing Local Metabolism. As previously stated, the application of heat directly to the hand or foot produces an enormous increase in the circulation, due to greater metabolic activity of the tissues. It occurs just as actively in an extremity deprived of sympathetic innervation as in a normal extremity (5, 6, 18). The increased blood flow greatly exceeds that which can be obtained by reflex or paralytic vasodilatation. For example, Abramson, Zazeela and Marrus give the following figures: For the foot: blood flow at 32°C., 4.9 c.c. per 100 c.c. of foot volume per minute; after reflex vasodilatation, 10.1 c.c.; blood flow at 45°C., 15.2 c.c.

The simplest way to apply heat directly to the feet is by means of hot foot baths. The temperature of such baths can be easily regulated and maximal blood flow to the feet is produced as long as the bath is continued. Dry heat at a carefully regulated temperature may also be employed, and has the advantage that it may be used for many hours at a time. Diathermy and short wave high frequency currents can also be utilized for this purpose.

When organic arterial disease seriously limits the amount of blood which

can flow to the foot, heat must be used cautiously. The seriously devitalized tissues of such a foot may be damaged by a degree of heat which the normal foot would readily tolerate. It has been found by clinical experience (19) that a temperature of approximately 95°F. produces maximum relief of pain and improvement in color. Satisfactory heaters which automatically maintain a constant temperature at this level are available.

Such a temperature-regulated heater placed over the lower extremities is one of the most effective means at our disposal for improving the circulation in the extremities. By this means an increased blood flow to the feet can be maintained for many hours without the danger of a burn. It may be used safely throughout the night while the patient sleeps.

When the circulation to an extremity is suddenly arrested, as by an embolism to a major artery, the use of even mild heat may be unwise. The stimulation to metabolism caused by heat makes demands upon the circulation which it may be unable to meet. Under such circumstances the suggestion made by Allen (20) that the metabolism of the tissues should be reduced by cooling the extremity deserves consideration. With the metabolism reduced by this means, the cells may survive in spite of a seriously curtailed circulation. After the collateral circulation has had time to develop, the temperature can gradually be raised to normal.

d. Vasodilatation by drugs which relax smooth muscle. The production of vasodilatation by reflex means, by paralysis of the sympathetic, and by increasing local metabolism has now been discussed. There is a fourth way of producing vasodilatation which differs from all of these. It is by the use of drugs which affect the smooth muscle of the vessel wall even when all nerve connections are destroyed. Perfusion of an isolated arterial strip by solutions containing nitrites results in relaxation of the vessel wall and widening of the lumen. Other drugs which cause vasodilatation are papaverine and theobromine. Papaverine is generally regarded as particularly valuable when embolism or thrombosis has produced a sudden occlusion of a major vessel. Its value has been questioned recently by Littauer and Wright (27). As has been previously stated, histamine is able to produce local vasodilatation. The choline derivatives, particularly acetyl-B-methylcholine chloride (mecholyl) have a similar effect (28). Both histamine and acetyl-B-methylcholine chloride are more effective when administered by iontophoresis to the affected extremity. Carbon dioxide foot baths may also be tentatively included in this group (29). The vasodilatation produced by histamine or mecholyl iontophoresis and by carbon dioxide foot baths is limited by the degree of penetration, and is probably confined to the skin. It is logical to use any of these drugs as adjuvants to other methods of treatment.

c. Venous Occlusion and Reactive Hyperemia. Of all the forms of treatment used for patients with peripheral arterial disease, none has been presented in more modifications than venous congestion. Seven methods

of utilizing this principle are listed in Table 1. All patients with advanced peripheral vascular disease soon learn that they can obtain some relief of rest pain by keeping the extremity in the dependent position. Thus many sleep with the foot resting on a chair alongside the bed, or else sleep in a chair. This position produces venous congestion and frequently results in undesirable swelling of the leg and foot. Buerger's exercises utilize the period of rest in the dependent position, but alternate it with periods during which the leg is elevated and then kept horizontal. By the faithful use of these exercises, considerable relief of pain can be obtained without producing the undesirable swelling. The recently devised oscillating bed (Sanders (31)) is a passive method of performing Buerger's exercises.

The last four methods listed in this section all attempt to produce complete venous occlusion. They differ only in details. In three of them a constriction is thrown around the extremity which theoretically obstructs the venous return without interfering with the arterial inflow. Any such constriction, however, must, to a certain degree, reduce the inflow of arterial blood. In the fourth method, venous occlusion is produced by direct ligation of the femoral vein.

In Bier's hyperemia an elastic bandage is used as a constricting band and is left in place for several hours. The major effect of this procedure is to produce venous stasis for a long period. As previously stated, the benefits derived from arresting venous outflow appear to be due to increased intravascular pressure. When the band is removed some reactive hyperemia develops and persists until the "blood debt" is repaid. The intermittent venous occlusion apparatus accomplishes the same purpose, but the constriction is applied only for a few minutes at a time instead of hours. As a result the phases of reactive hyperemia are multiplied. The suction-pressure glass boot apparatus is a more complicated means of accomplishing the same purpose. When air pressure within the boot is diminished, it is equivalent to an increase of air pressure to the outside of the boot. Since the only non-rigid part that can yield to this relatively increased pressure is the rubber cuff around the thigh, the net effect is nearly similar to that of the intermittent venous occlusion apparatus (21). The minor differences in this method are that the diminished pressure on the surface of the extremity may allow a slightly greater filling of the superficial vessels, and the subsequent positive pressure on the surface aids in squeezing out the blood accumulated in the extremity. Femoral vein ligation differs from the other methods in that reactive hyperemia is not produced.

The writer has had considerable opportunity to study the effects of these four methods of treatment and has found them to be almost equivalent. They all appear to have value in aiding the healing of ulcerative lesions (22). Theoretically they should all aid in the emergency treatment

of patients who have had an acute embolic or thrombolic occlusion of a major peripheral artery. In my experience there has been little evidence up to the present that the circulation is permanently improved or that intermittent claudication is relieved by these methods. Others have reported more enthusiastically on the merits of these appliances. Other factors which may be responsible for the improvement noted (15) should be carefully investigated.

f. Inflammation. The use of inflammation to produce an increase in blood flow to an extremity occupies a minor place in the treatment of peripheral vascular disease. Mustard foot baths may be regarded as an example of this principle of treatment. The application of mustard to the skin results in redness, and if allowed to remain too long blistering and serious burns may result. Mustard may therefore be regarded as an irritant which produces inflammation. Killian and O'Classen (9) have shown by plethysmographic studies that mustard foot baths greatly accelerate blood flow to the extremities at temperatures between 35 and 40°C. At higher temperatures water baths were as effective as mustard baths.

g. Exercise. Exercise as a means of increasing the circulation in the muscles has not been sufficiently utilized as a method of treatment. On the contrary, most patients with peripheral vascular disease are advised to refrain from exercise, and to spare their legs in every way. A marked increase in blood flow in the muscles after exercise has been reported by various investigators. It has been my practice for years to encourage exercise, such as walking, riding a bicycle, playing golf, tennis, or handball, and swimming. Striking improvement in the ability to walk frequently follows the use of regular exercise. The prescription to walk a mile or more three times a day is often more effective in improving intermittent claudication than any other form of treatment.

h. Intravenous Injections of Hypertonic Solutions. I have reserved until the last the discussion of intravenous injections of hypertonic salt solution. Although I have used this form of treatment more than any other (23), and have found it more dependable than other methods, I am not certain of the principle by which it improves circulation. Long clinical experience has convinced me that it is one of the most effective methods of developing collateral circulation. Of all the methods of treatment which we have studied it is one of the few which is followed by elevation of both skin and muscle temperature (1). It produces an increase of blood volume for a few hours, and an increase in cardiac output (24). The salt injected is excreted slowly over a period of forty-eight hours; it is temporarily stored in the soft tissues and thus produces a relative hydremia. I suspect that the latter effect has much to do with its value in aiding collateral circulation to develop in these tissues. In any case, it appears to be a method of treatment which depends upon a different principle from all those previously mentioned.

DISCUSSION

The foregoing analysis of various forms of treatment does not, of course, include all the methods which have been proposed or used. However, such an exhaustive discussion is not necessary to emphasize the

TABLE 1

Various Measures for Increasing Blood Flow

By reflex vasodilatation
Blankets
Hot drinks
Electric heating pads, hot water bottles
*Baking apparatus
*Hot baths
Diathermy and short wave
Fever resulting from intravenous injections of typhoid vaccine or other foreign protein
Fever produced by physical means
By paralytic vasodilatation
*Drugs—sedatives—alcohol
Perivascular sympathectomy
Sympathetic ganglionectomy
Paravertebral injections of alcohol
Adrenalectomy
Arteriectomy
By increasing metabolic activity of tissues
Hot foot baths
*Thermo-regulated heating cradle
Diathermy and short wave
By drugs which relax smooth muscle
Nitrites
*Papaverine
*Theobromine
Histamine iontophoresis
Mecholyl iontophoresis
Carbon dioxide foot baths
By venous congestion and reactive hyperemia
Dependent position of leg
*Buerger's Exercise
Oscillating bed (Sanders)
Bier's hyperemia
*Intermittent venous occlusion apparatus
Suction pressure apparatus (Pavaex)
Femoral vein ligation
By producing inflammation
Mustard foot baths
**By exercise*
**By intravenous injections of hypertonic salt solutions.*

point of this paper. Enough has been stated to show that many forms of treatment which at first glance appear to utilize different principles, are in reality only different methods of utilizing the same principle. It follows naturally that in the interest of the patient the simplest, safest, and least

expensive of the various means of using any one mechanism should be selected. If it is desired to use more than one means of increasing circulation, different principles of treatment should be selected. The methods which seem most useful to the writer are starred in Table 1.

It is scarcely necessary to point out that our knowledge of the physiology of the peripheral circulation is very limited at the present time. As investigations continue in this interesting field, new principles will undoubtedly be revealed, and perhaps more efficient methods of treatment will be discovered. Much more remains to be learned about the relative efficiency of the measures already used for increasing the peripheral circulation. With better understanding and greater experience it will be possible to discard those which have little value, and to select methods which are most effective in utilizing the physiological mechanisms available.

SUMMARY

Eight fundamental methods for improving the circulation in the extremities are discussed. Some of the measures now employed in the treatment of patients with peripheral vascular disease are analyzed to determine the principle underlying each form of treatment. It is demonstrated that many methods duplicate each other by utilizing the same physiological mechanism.

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A SUPRACHOROIDAL IRIDOTASIS FOR CHRONIC GLAUCOMA

A Preliminary Report

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The various operations for chronic glaucoma which give filtration fistulae will yield some success if properly performed. The question of acute glaucoma is not being considered at all, for no other operation is so satisfactory as the broad basal iridectomy which, however, is of no value whatsoever in chronic simple glaucoma unless there are inflammatory symptoms.

In 1927, the writer found that no operation was succeeding uniformly in chronic glaucoma. Cyclodialysis was being performed more than any other type of operation, with good results in some cases but with poor results in others. The Elliot trephine operation was probably giving the best uniform results of any used but, because of late secondary infection, it was not being used as generally as was considered advisable. Since the logical anatomical drainage within the eye is suprachoroidal, it was felt that an operation which leads to subconjunctival drainage is not only mechanically at fault but by leaving the iris exposed underneath the conjunctiva invites the danger of possible secondary infection or even iridocyclitis and uveitis.

Cyclodialysis is a very good operation but was found not always successful or permanent because the root of the iris will re-attach unless iris pigment has been left at the point of separation in the wound so that drainage is established. This principle is the same as in a root iridectomy, in which pigment is left at or near the scleral edges thus, giving good drainage into the suprachoroidal space.

The majority of the so-called filtration operations such as root iridectomy, iridoencleisis, trephining, etc., have in common one danger: some injury to the capsule or zonule of the lens causing a late complete or partial cataract. This is especially true if the anterior chamber is very shallow. When such a cataract develops, it becomes very difficult to perform a cataract extraction with safety or ease.

With these ideas in view, it was decided in 1927 to attempt an operation which would combine cyclodialysis with a suprachoroidal iridotasis to keep the drainage wound open permanently. This operation was performed on three cases of chronic glaucoma, one being a rather severe case which had previously had two other types of operations performed without success,

the tension remaining elevated to 60 (Schiotz). The results were uniformly successful and the operation was, therefore, performed successively upon some private patients with the same uniform results.

In this operation a sclerotomy is performed first, followed by a cyclodialysis and finally iridotasis into the wound, the iris being left in the suprachoroidal channel or wound. It is simple to perform and it is safe since with reasonable care there can be no damage to any of the tissues.

The technique first used was as follows: The conjunctiva is dissected free after a vertical incision temporally, about 7 mm. from the limbus. The sclera is then exposed and a rounded keratome is used to dissect very carefully, a vertical section 5 mm. long, about 7 mm. from the limbus and parallel to it. This is the most important part of the operation since care must be exercised to prevent any injury to the underlying choroid. The choroid should be exposed throughout the whole length of this incision. A heavy iris repositor, bent at an angle of 40 degrees is then used to separate the choroid and ciliary body from the sclera, finally entering the anterior chamber. The point of the repositor at all times should be in contact with the sclera and close to the posterior surface of the cornea. If this is carefully observed, no injury can occur to any intra-ocular structures. A free and wide cyclodialysis of 4 mm. is then made at the iris root. An iris forceps, very thin and round, with a curve of 40 to 45 degrees is then introduced and the pupillary margin of the iris is grasped and drawn into the cyclodialysis channel. The iris is twisted slightly to obtain a "wick" action. Ordinarily, considerable amounts of iris pigment come out with the iris forceps and remain on the edges of the sclerotomy wound. The conjunctiva is then sutured and atropine instilled to allow the iris to stay as it was placed. Care should be exercised to prevent scraping the posterior surface of the cornea with either the repositor or the iris forceps.

The reactions following the operation are usually very slight and not more than those following an iridectomy. There is generally an immediate, sharp reduction in tension; this is especially noticeable in the secondary types of glaucoma, the tension in one case dropping from 80 Schiotz to 12 Schiotz. Results have been uniformly satisfactory. It should be pointed out that the operation was used originally on cases which had been previously operated on without any success, and in which visual results were not expected. Later, when cases of chronic simple glaucoma were operated upon by this method, visual results were expected. In no case has there been any of the late complications that usually follow glaucoma operations.

Heine in 1905 advised cyclodialysis for chronic glaucoma, the intent being to produce an internal fistulization between the anterior chamber and the suprachoroidal space. Many surgeons have used the operation with success. Others have not been so satisfied with the results.

In 1929, Mauksch (1) published a paper modifying cyclodialysis with the intent to keep open the canal by interposing the iris into the canal and

prevent its closure. His operation was performed a little temporal to the vertical meridian and the scleral incisions was made from 5 to 6 mm. from the limbus. In none of his cases was filtration demonstrated. In 1931, Suker (2) reported his results in fifteen cases performed according to the Mauksch method. In 1935, del Barrio (3) reported about 39 cases in which he used a blunt hook to engage the iris instead of pulling it out with forceps. He also resected the pupillary margin to prevent the iris from being drawn back into the anterior chamber. In 1940, Troncoso (4) published a paper with another modification of cyclodialysis. He inserted a piece of magnesium into the channel in order to keep it open.

The operation described, differs from the Mauksch method in several respects. 1) the test for permeability is made with the use of fluroscein which is then observed in the anterior chamber. In two of the cases which had this operation, subconjunctival injections of fluroscein were visible with the slit-lamp microscope in the anterior chamber within a period of seven minutes in one case, and twelve minutes in the other. It is the the opinion of the author that unless such permeability is obtained, fistulization, no matter what its type may be, is a failure.

2) The incision is made temporal to the limbus and anterior to the insertion of the external rectus muscle. The pull of this muscle seems to keep the scleral wound open and assist in the drainage. At no time, however, has there actually been a bleb observed at the site of the sclerotomy, although there was definite evidence of such fistulization as shown by the fluroscein test. The constant traction of the external rectus muscle upon its insertion, keeping the wound open and preventing complete closure, is of great assistance, in the opinion of the author.

3) A definite attempt is made to traumatize the iris so that the pigment epithelium is loosened and dislodged, thus aiding the permanency of the fistulization, by regeneration along its tract.

Complications. 1) Injury to the lens. This is probably the most frequent complication. The tendency to protect the posterior surface of the cornea as much as possible may result in injuring the lens. It may also be injured if too large a bite is taken with the iris forceps in grasping the lens capsule.

2) Injury to the choroid and ciliary body, with or without hemorrhages. This is avoided by careful sclerotomy, careful manipulation of the repositor or spatula, and careful use of the iris forceps. As stated, great care should be taken in keeping the point of the iris repositor or forceps in close contact with the sclera and as close as possible to the posterior surface of the cornea.

3) Injury to the cornea. If the point of the forceps or iris repositor is allowed to scrape the posterior surface of the cornea, injury to the endothelium and Descemet's membrane may occur and cause some clouding of the cornea. This was seen in one case. It promptly cleared up in five days.

Other complications, such as loss of vitreous, prolapse of the choroid, etc., have not been encountered.

The series of cases since 1927 has included all the glaucoma cases seen by the author both in private and hospital practice. The operation has been limited entirely to those cases of glaucoma in which there are no acute or inflammatory symptoms.

Results. The cases encountered number 149 but it is impossible because of lack of space to tabulate them in detail. Of this number 49 were bilateral cases, each eye being considered as a separate and distinct entity. Consequently there were, 51 cases other than these 49 cases totalling exactly 100 patients operated on until the first of this year. Of this total number of patients, 77 have been followed for a period of three years at least, some of the earlier cases having been observed for twelve or thirteen years.

In the first 37 operations, visual results were not expected since the vision was lower than 10/200 in practically every case. In every one of these patients, however, whatever vision was present before the operation was retained. There was no diminution in central visual acuity nor any further progression in the loss of the fields.

In the later cases, 112 operations were performed where the vision varied from 20/20 to 20/200. In eight of these cases there has been some slight deterioration due to secondary changes in the lens, which were probably developing at the time of operation. The fields of vision have not been further impaired in any case.

The average reduction in tension was 21 points Schiotz; the tension has remained within normal limits in 97 per cent of these operative cases. In the remaining 3 per cent there have been some transitory rises in tension due to various extraneous factors such as emotion or some unexplained cause.

Conclusion. It is the belief of the author that this operative procedure offers the greatest source of probable relief for chronic glaucoma. The author has in all of these cases continued the use of cycloplegics after the first two weeks of operation and feels that they should not be abandoned. It is his desire to see a substantial and large group of glaucoma patients operated on by this method and the results published for corroboration.

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TWO CASES OF SUCCESSFUL SUTURE OF PENETRATING STAB WOUNDS OF THE HEART[1]

With Some Observations on the Subject

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Cases of penetrating stab wounds of the heart are frequently regarded only in the light of their dramatic quality, but they present many points of clinical and surgical importance and of interest in thoracic physiology and surgery.

CASE REPORTS

Case 1. History. O. W., a 25 year old colored woman, was admitted to the Harlem Hospital on December 25, 1939 at 5:15 p.m. She was in mild shock, conscious and rational. She had been stabbed in the chest. The exact time of the stabbing and the instrument used were not known. Two half-inch wounds were present on the anterior portion of the left chest. One was in the fourth intercostal space, two inches from the sternal border, the other in the fifth intercostal space, three inches from the sternal border. There was slight bleeding. The blood pressure was unobtainable.

The patient was seen by the author about three-quarters of an hour after admission. Her condition seemed to have improved since admission. The pulse rate was 134 per minute, soft and regular. The blood pressure was 80 systolic and 50 diastolic. The left border of the heart was percussed just lateral to the midclavicular line in the fifth intercostal space. The heart sounds were muffled. A roentgenogram of the chest showed diffuse enlargement of the pericardial shadow and a shadow in the lower portion of the pleural cavity. This picture was interpreted as hemopericardium and hemothorax.

A diagnosis of penetrating stab wound of the heart was made, but because the patient was improving under observation and had reached a stage where she was quite comfortable and her condition was fair, it was thought advisable to observe her for further improvement rather than to operate upon her. However, at about 6:45 p.m. she became worse rather suddenly, showing signs of collapse. The blood pressure dropped to 60 systolic and 40 diastolic, pallor was noticeable, the pulse could not be felt, and the heart sounds became rapid and feeble. The patient experienced syncope and the extremities became cold. These signs increased in intensity. Operation was then decided upon and performed at 7:10 p.m.

Operation. A C-shaped incision was made encircling the mesial half of the left breast down to the ribs. The breast and the underlying pectoralis major muscle were retracted laterad in one flap. About three inches of each of the fourth and fifth ribs were removed at their sternal ends, together with the adjacent intercostal

[1] Read before the New York Surgical Society, May 8, 1940.

muscles and pleura. The pieces of rib were discarded. This produced an opening into the pleural cavity about three inches square. The lung was grasped in a sponge forceps and held in the upper part of the wound. The internal mammary artery was ligated at the superior and the inferior limits of the opening in the chest wall. The pericardium showed a penetrating wound from which there was a slight flow of blood and 600 cc. of blood were found in the pleural cavity. A long vertical incision was made in the pericardial sac within which there was about 80 cc. of free blood and clot. The heart beat rapidly and feebly. The musculature was in marked contraction, dilating only slightly on diastole. There was a penetrating wound about five-

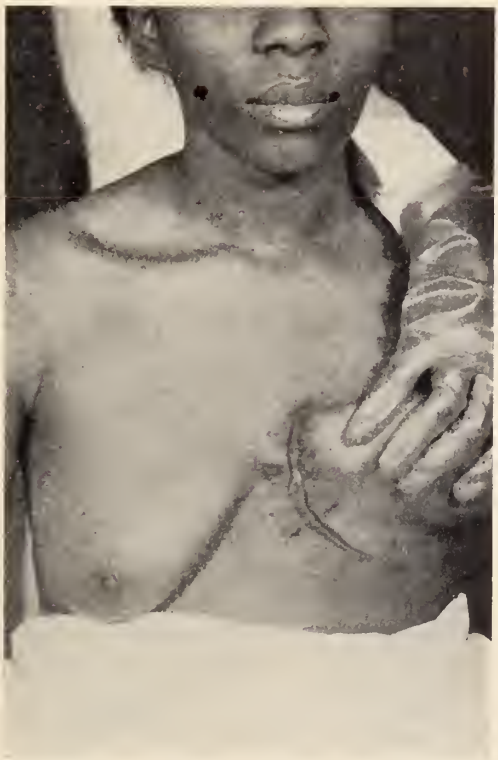

FIG. 1. Case I. When the breast is in its normal position it covers the operative area. There is no herniation of lung in any of these cases.

eights of an inch long in the right ventricle situated midway in the course of the anterior descending coronary artery and about a half an inch from it. Very little blood came from the wound, not only because the cardiac musculature, held mainly in systole, contracted in such a way as to close the wound but also because the patient had lost considerable blood. A blunt probe was passed through the wound into the right ventricle and this occasioned some bleeding. The heart was brought forth with the palm of the hand.

One figure of eight suture of silk was sufficient to close the cardiac wound. The pericardial sac was not closed. The window in the chest wall which had been produced by removal of sections of rib, etc. was closed by suturing the lower lobe of the left lung to it (Fig. 5).

During the operation the patient was given an intravenous injection of physiological saline solution and citrated blood which was continued after operation as needed. For prophylaxis, an injection of gas bacillus (mixed) antitoxin and sulfanilamide (120 grains a day for three days) were given.

Postoperative Course. The convalescence, except during the first twenty-four hours, was uneventful. The patient's temperature rose to 104.4°F. the first day. For the next three days the average temperature was 100°F., then it became normal and remained normal. Except for asthenia there were no complaints. She was kept in bed for three weeks in order to give rest to her heart muscle.

She was seen five months later. She then said that her condition, except for slight weakness, was very good. She had almost reached her normal strength.

Case 2. History. C. T., a 19 year old colored girl was admitted to the Harlem Hospital on January 18, 1940. On admission at 9:40 p.m. she was in severe shock. No heart sounds were audible or pulse palpable. The systolic blood pressure was 0, the diastolic 0. There was a ragged 2 cm. laceration at the level of the left second rib near the anterior axillary line. The pneumothorax reading in the left chest was minus 3, minus 1. In a short while the pulse became palpable, though of poor quality, and the heart sounds, together with the almost continuous bruit characteristic of air and fluid in the pericardial sac, became audible. The blood pressure rose to systolic 94 and diastolic 52. For a period of approximately three-quarters of an hour she seemed to be recovering from shock and then rather rapidly became worse. The blood pressure became lower, the heart sounds became weaker and irregular and the patient became faint and pale. Because of the succession of events, i.e., 1) *shock*, 2) *improvement*, 3) *shock*, it was thought advisable to operate for laceration of the heart although the point of entry of the chest wound was at some distance from the cardiac area. The breasts were large and flabby and it was therefore conceivable that the assailant's knife, entering the skin high up on the chest, may have been pressed down with force upon the easily movable breast to enter the chest cavity at a much lower point than the skin laceration would indicate.

Operation. This was performed through a C-shaped incision which followed the mesial aspect of the left breast and was carried through to the ribs. The breast and the pectoralis major muscle were reflected in one mass from the ribs. The lower border of the third rib had been lacerated about three inches from the mid-sternal line and the opening into the chest cavity was in the third intercostal space. About two inches of the third, fourth, and fifth ribs were removed from the sternum *laterad*. The pieces of rib were discarded together with the attached parietal pleura. This procedure produced a large opening into the pleural cavity allowing for easy observation of the contents. There was a half inch laceration through the lower lobe of the left lung near the mesial border. It was not sutured. The lung was grasped in a sponge forceps and held in the upper portion of the wound. The pericardial sac had been lacerated and blood trickled from it. There was about a pint of blood in the pleural cavity. The pericardial sac was opened through a long vertical incision anterior to the phrenic nerve. Because of the thick chest wall the heart was at more than the normal distance from the skin surface. There were two bleeding lacerations of the left ventricle. One was about 1 cm. and the other about 1.5 cm. in length. One was about 2 cm. and the other about 3 cm. from the anterior descending coronary artery in its middle third. The heart was in marked systolic contraction showing only a small excursion with diastole. A suture was placed in the apex, traction was applied, and the bleeding ceased. Each wound was closed by two silk sutures. While a suture was being applied to the posterior heart wound which was deep and on the postero-lateral surface of the left ventricle a 1.5 cm. portion of needle broke off and remained in the cardiac musculature. It was not palpable and was not recovered.

The heart was replaced in the pericardial sac which was not sutured. Blood was aspirated from the posterior portion of the sac and from the pleural cavity. The lower lobe of the left lung was sutured into the operative defect in the chest wall which had been produced by the removal of portions of ribs. This completely closed the orifice. The flap consisting of breast, skin, and muscle was then sutured in place. A small gauze drain was placed down to the bony chest wall.

Postoperative Course. After operation the patient was given frequent transfusions, sulfanilamide, fluids parenterally and intravenously and sedatives as required. The immediate response to operation was good but complications followed. The next morning her condition became poor, the pulse was rapid (160 a minute) and

FIG. 2. Case 2. Note the large breast which can be drawn well away from the cardiac area after the C-shaped incision is made.

thready and the respirations rose to 60 a minute. The condition was relieved by repeated aspirations of air under tension in the left pleural cavity until the pressure became negative and remained so. Severe precordial pain was constant during the first week. The patient seemed then to improve gradually until two weeks after operation when she became apathetic, restless and quite toxic. For three days the toxic state became worse. She did not speak freely and remained apathetic and lethargic. Then gradually the condition improved so that by February 10, she appeared normal. During the toxic phase the blood urea-nitrogen was 45 (February 2) and 85 (February 5) and the blood creatinin 3 (February 2) and 2 (February 7). On February 7 the blood chemistry figures were normal. The patient had received sulfanilamide for seven days after operation at the rate of 6 grams a day.

On March 1, she suffered a fall from her bed to the floor with no untoward result.

The temperature ranged between 101 and 103.5°F. the first week, 100 to 102°F. for the next three days, when it rose to 102 to 104°F. for the second week. A large abscess was found in the anticubital fossa at the site of infusions and transfusions. With the evacuation of pus from the abscess the temperature returned to normal.

Follow-up examinations five months after operation revealed no complaints except for the fact that the patient had not quite recovered her full muscular strength.

In both cases electrocardiagrams at first showed changes characteristic of coronary occlusion, but within four months they were normal.

DISCUSSION

In the cases here recorded, as well as in others, we have been able to make the following observations, some of which have already been made by others.

It is impossible to tell from the location of the stab wound in the skin whether the heart has been injured or not. The knife blade pierces the skin and may be pushed in any direction. Even a short blade may be inserted to a considerable depth and with great force against the more or less elastic chest wall. Flabby soft tissues of the chest wall, especially the female breasts, allow for great mobility, so that the knife may enter the skin, then move the soft tissues to such an extent that the knife enters the pleural cavity or the pericardial sac a few inches away. In the majority of cases a right handed assailant strikes the victim's left anterior chest wall and the direction of the knife blade is downward and mesial. The distance of the skin wound from the pericardium is not necessarily a criterion in deciding whether the heart has been injured. We have seen cases of penetrating wounds of the ventricles of the heart in which the skin was entered as high as the second rib and as far laterally as the mid-axillary line.

Patients with penetrating wounds of the heart may recover without operation. It is possible in some cases for the bleeding to stop due to a moderate but sufficient cardiac tamponade. The laceration heals and the blood in the pericardial sac is slowly and completely absorbed. Therefore, patients may be treated symptomatically as long as they show improvement but as soon as they show signs of increasing cardiovascular collapse, operation must be done without delay. The changes in clinical appearance, pulse, blood pressure, and respirations will determine the course of action.

Cardiac tamponade may save life or cause death. When cardiac tamponade occurs the laceration in the pericardial sac is closed by a blood clot. This clot may arise from the blood in the pericardial sac and become lodged in the orifice produced by the laceration, or the clot may arise in the pleuropericardial wall surrounding the lacerated portion and close the orifice by encroaching upon it very much like the shutter of a camera. If the clots are not dislodged there are two possible eventualities. Blood coming through the heart wound may be small in quantity but, caught

between the heart and pericardial sac, it may be under pressure strong enough to cause the wound to close, thus preventing further bleeding and allowing the wound to heal. If, however, the blood comes continuously from the lacerated heart and cannot escape from the pericardial sac which has been closed, the pressure within the pericardial sac rises to such an extent that the heart cannot dilate normally. Gradually diastole becomes more and more limited until no more blood can be drawn into the heart. Indeed, if blood were present in the chambers of the heart it could not be distributed to the arteries because the marked pressure of the tamponade prevents systolic contraction and, strangling the heart, causes death.

Shock, improvement, shock. In bleeding from the heart and, indeed, from any blood vessel the sequence of shock, improvement, and shock may occur. This usually means that from trauma and loss of blood the patient may show signs of shock. The patient may show improvement with rest, warmth, morphine and intravenous administration of physiological salt solution and blood. The improvement may be short lived, however, because the increased muscular action accompanying the improvement may cause increased hemorrhage, frequently causing death. Blood clots may have been expelled from the heart wound or from the pericardial wound, allowing free egress of the heart's blood. When a patient enters the hospital it may be impossible to tell from the history and physical findings how much blood has been lost. It is difficult to say what the margin of safety may be. Therefore, death may follow because we are unable to treat promptly or adequately the shock due to hemorrhage which follows apparent improvement.

Injury to pleura. Some observers indicate that penetration of the pericardial sac and the heart occurs from stab wounds without traversing the pleural cavity. This is, of course, possible within the cardiac incisura or undefended space. In our experience this has been purely theoretical since no case has failed to show laceration of the pleura. In most cases the undefended space is extremely small so that we may take it for granted that the pleural cavity has been entered. Indeed, when we consider the usual direction of the knife blade, that is, downward, we should expect that when a knife enters the undefended space it will miss the chambers of the heart. Since most of the cases will have pleural injury we must bear in mind the complications that may occur in the pleural cavity and we must be prepared to prevent them or to watch for them and take care of them as they arise before or after the operation. The main complications in the pleural cavity are hemothorax, tense pneumothorax, and infection.

In one instance a piece of needle imbedded in the wall of the left ventricle (Case 2) caused no subjective symptoms after a short period of postoperative precordial pain. From the experience of others, a foreign body may remain imbedded in the heart wall for years without symptoms.

Operative procedures. We have found certain advantages in the operative procedure herein described. The approach to the heart is facilitated because the window made in the chest wall is large and quickly formed, and the closure is easily made. The attachment of the lung to the chest wall is important in that it fixes the mediastinum so that it does not move in respiration. This prevents a disturbance of the cardio-pulmonary stability which is important for proper functioning of heart and lungs. The complete closure of the window in the chest wall by means of lung tends to prevent tense pneumothorax, although occasionally this may

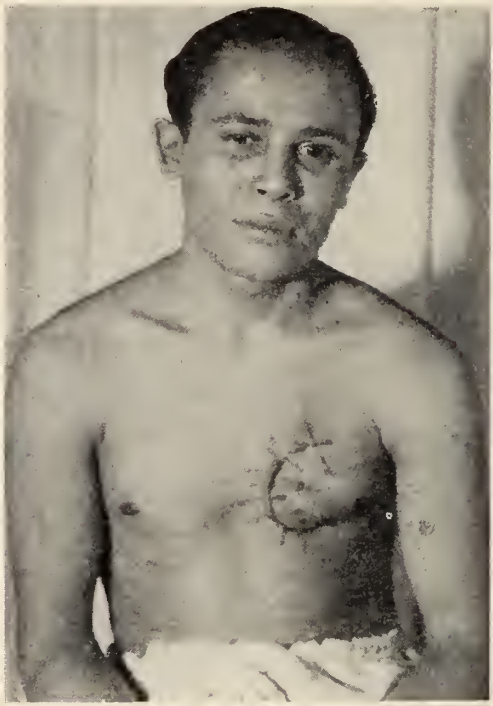

FIG. 3. The entire extent of the incision which can be seen better in this male patient whose case was previously reported (New York State J. M., 36: 23, 1936).

occur by way of a stitch hole in the lung. The importance of mediastinal stability may be seen frequently during operation when the pleural cavity is wide open. Sometimes, when the lung collapses and the mediastinum flaps, the lungs may cease to move and the heart may stop beating. When this happens function may be restored by grasping the collapsed lung in a sponge forceps and pulling it out to the chest wall away from the mediastinum. For this reason, the lung is always grasped in a sponge forceps and held out of the wound to maintain mediastinal stability during the operation.

The methods of handling the heart are variable. "Palming", by means of which the heart is held in the palm in such a way that the base of the heart is grasped between the index and middle fingers, has not been satisfactory in our experience. While it may stop the flow of blood through the laceration it tends to cause *delirium cordis* and even cessation of heart action. A more efficient method has been that of traction by means of a

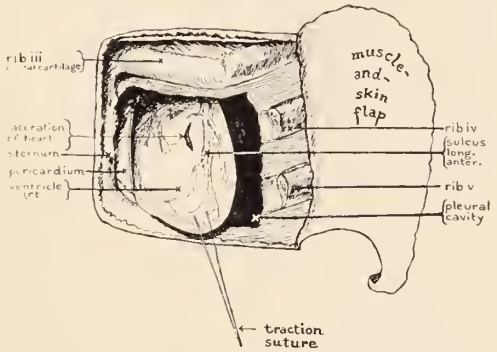

Fig. 4. The operative approach and the findings in Case 1. In Case 2 the operative approach was similar, but the wounds were in the left ventricle deep in the pleural cavity. The window in the chest wall is shown with the heart drawn forth by a traction suture.

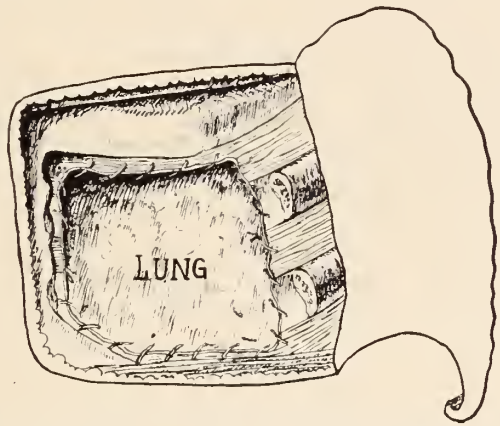

Fig. 5. The lower lobe of the left lung has been sutured against the window in the chest wall so that it effectively closes it. The muscle-and-skin flap is then sutured back in place over it.

suture placed through the thick muscular apex. When the heart is then drawn forth from the pericardial sac and held with moderate tension, bleeding is controlled, the heart beat is not interfered with, and the sutures may be passed easily, the operator using both hands while an assistant produces the traction. It has been recommended that the sutures in the heart wound be tied during diastole. This is theoretically sound. Prac-

tically it is difficult to pick out the diastolic phase. Practically, also, it is not necessary since it will suffice to tie the suture in either phase snugly but never tight. Bleeding is easily controlled even with a moderately loose suture. The suture material should be fine and supple. For that reason silk is preferred to cat gut. As far as the premature absorbtion of cat gut is concerned we need have little fear, since healing of the lacerated heart takes place rapidly enough. In specimens taken from patients who died forty-eight hours after operation we have found a fairly good agglutination of the opposing surfaces of the laceration. No patient observed by us died because the sutures were incompetent.

The needle should be of the fine "intestinal" type. The so-called "non-traumatic" needle is excellent. If a large caliber needle is used it may produce holes in the heart muscle big enough to cause more bleeding which will require further suture to control it.

The heart muscles of various individuals differ greatly as to friability. For that reason needles and sutures should be placed with care and putting the finger in the lacerated heart wall to stop hemorrhage should be avoided.

Closure of the pericardial sac is inadvisable. We have observed serum and blood in the pericardial sac after closure become infected and require drainage. If the pericardial sac is allowed to remain open, drainage into the pleural cavity will take place. In the pleural cavity serum and blood whether infected or not will cause less trouble and may be more easily drained than in the closed pericardial cavity. In the pericardial cavity symptoms of pressure (tamponade) as well as of infection may result from the retention of serum or pus.

The *internal mammary artery* and vein demand special attention. Their position close to the sternal border directly over the heart makes them vulnerable both in the stabbing and during operation. These vessels are surrounded by very little soft tissue and therefore when cut cannot retract as well as most blood vessels which are surrounded by muscle. Their mouths tend to remain open and they may easily bleed into the pleural cavity, since the parietal pleura, close to it, is severed together with the vessels. It is possible for the severed vessels not to bleed during the operation because much blood has been lost and the arterial pressure is low, but when the operation is finished and fluid and blood have been administered intravenously, the arterial pressure is increased enough to cause further bleeding and sometimes death. The cut vessels bleed into the pleural cavity as into a huge receptacle. In all cases, therefore, the internal mammary vessels should be isolated and ligated at the superior and inferior borders of the operative field, because it will be remembered that the artery as well as the vein can bleed from either end.

In the postoperative treatment sulfanilamide has proved very valuable. It should be given immediately on admission and continued in sufficient dosage for three or four days. Infection, usually with a streptococcus, was one of the commonest complications prior to the use of sulfanilamide.

Morphine should be given as often as necessary and in sufficient dosage to keep the patient quiet. It helps to prevent exhaustion by stopping the extreme muscular and mental activity so common after operation. The heart is thereby rested.

In cases of dyspnea, the oxygen tent should be used. All our patients were placed in oxygen tents immediately after operation as a prophylactic measure.

Fluids, blood and physiological salt solution should be given in quantities sufficient to maintain the blood pressure at a normal level. Care should be taken not to give too much fluid to the patient who has not lost much blood, since the heart may be overloaded and death may occur from pulmonary edema. Blood is, of course, more effective than salt solution and in the cases where there has been great loss, 1000 cc. may be given within a few hours after the operation. The intravenous apparatus should be attached before the beginning of the operation and kept in place as long as necessary.

Tense pneumothorax may cause distress after operation and even contribute to death. Therefore, at least once a day for the first three or four days a pressure reading of the pleural cavity is made. If there is present a tense pneumothorax, air is removed and the readings are repeated every five hours until a negative reading is obtained. If the tense pneumothorax does not respond to the frequent tappings, a continuous tube drainage of air is made.

The most frequent causes of death after penetrating stab wounds of the heart are hemorrhage and infection. Other causes form a very small percentage of the total. Hemorrhage may frequently be fatal before the patient can be brought to the hospital, or while he is on the operating table, because the flow of blood may be greatly increased upon opening the pericardial sac and cannot be stemmed in time. Later on, due to the collapse caused by primary hemorrhage and the shock of operation, the patient does not respond to treatment. Death may result from a comparatively small amount of blood in the pericardial cavity causing a tamponade which strangles the heart. Finally, secondary hemorrhage from an unrecognized severed internal mammary artery has been a cause of death. The heart in these cases is found at post mortem in a state of marked contraction with the chambers empty of blood.

Before the advent of sulfanilamide, infection frequently caused death. Since then, however, there seems to have been a lower mortality. The number of cases has been too small, however, to draw conclusions as to the effectiveness of the drug. When infection does produce death it is usually not a localized affair. Most often it involves, by direct extension, the pleural cavity, the pericardium, the mediastinum and thence produces a sepsis.

HORMONAL AND SURGICAL TREATMENT OF UNDESCENDED TESTES

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The question of the undescended testis has become controversial in a new sense since anterior pituitary hormone was introduced to accomplish its descent. The first report of the results with this therapy was published by Shapiro (1) in 1930. Before that the controversy was confined to the question as to whether an undescended testicle should be operated upon. Today the question is should such a testis be treated by injection of hormone or should it be operated upon.

In the first controversy the arguments advanced against operative interference were: 1. The testis is doing no harm in its abnormal location. 2. It secretes its hormone. 3. Operation may result in atrophy and no hormone will be formed. 4. "Cosmetic considerations may be summarily dismissed" (Drake (2)). 5. "Psychic effect . . . scarcely merits serious consideration" (Drake). 6. Functionally one normal testis is as effective as two.

The arguments for orchiopexy[1] which are still valid, are: 1. If the testicle is placed in the scrotum before puberty it will not only produce its hormone but will also form sperm. A bilateral cryptorchid is sterile. 2. Malignancy is fifty times as common in the undescended testis. This is derived from the fact that the incidence of undescended testis in the population is one in five hundred and ten per cent of all tumors of the testis are in this group. 3. The undescended testis is more liable to strangulation, torsion, chronic inflammation and trauma. 4. Epididymitis of the scrotal testicle may leave the unilateral cryptorchid sterile. 5. Every cryptorchid is psychologically handicapped. 6. An operation has been developed in which atrophy results in only ten per cent of the cases. Therefore, it may be concluded that it is desirable to try to get the testis to reside in the scrotum.

The efficiency of the injection treatment is still questioned by some. However, no one should object to such treatment in the attempt to obtain descent of the testis, provided one resorts to operation if descent does not occur. Furthermore, one should not postpone operation beyond puberty for the sake of injection therapy because it is well recognized that the testicle brought down after puberty may not be spermogenic. The

[1] Word shown to be correct by Franz Torek: Ann. Surg., 94, 97, 1931.

undescended testis will function once it is placed in the scrotum. This should be an answer to the thesis that such a testicle is abnormal and because of that did not descend. Histologically there is no difference between the undescended and the scrotal testis before puberty.

Before the efficiency of hormone therapy is discussed it is necessary to agree on a definition of undescended testicle in order to have some criterion upon which to base the effectiveness of the treatment. An undescended testis is one that does not enter the scrotum under any condition. Hamilton and Hughes disclose that only six out of sixteen cases referred to them by pediatrists were true cryptorchid. The other ten were cases of "spastic retention" or "physiologic intermittent retention". Thus, ten of their patients might easily have been classed as "late spontaneous descent" or successes following hormone therapy. They propose a test to differentiate the true from the spastic. They apply a hot water bag to the scrotum, the inguinal region and the perineum for thirty minutes, in order to relax the muscular spasm that causes retraction of the testis. If everyone did this there would be fewer "late spontaneous descents" and fewer "successful descents following injections", and one would not see a testis descend six hours after injection, as reported by Cohn (3).

It is evident that if there is sufficient hormone in the body to cause one testis to descend the lack of descent of the other is not usually due to hormonal deficiency, but probably to anatomical conditions. This conclusion seems to be borne out by the experience of Hess and Kunstadter (4). They suggest the use of a hormone test of the urine to select those cases which are to be treated by injection therapy. With their form of selective treatment they obtained descent in twenty-five of their bilateral cases but in only three of their nine unilateral cryptorchids.

Emphasis has been placed on the value of hormone therapy as preoperative medication because it causes enlargement of the testes even though it may fail to bring about their descent. There is no doubt that the testicles and penis grow under the influence of the anterior pituitary hormone, but, in no case of bilateral cryptorchidism did I note an enlargement of the scrotum following injections. In one such case (J. W.), the scrotum enlarged only after the first stage of the Keetley-Torek operation was done on the first side. The second testis grew so large that it created a problem when it came time to place it under the skin of the thigh.

Endocrine therapy has other dangers and, therefore, the patients must be carefully followed. Although Turner (5) stated "Endocrine therapy is simple, without apparent harm," Thompson and Heckel (6) said that they "have been struck more by the influence of anterior pituitary hormone substance on the growth of the genitalia than by its influence on the descent of the testis." They reported that in the course of treating thirty-

three patients for undescended testis with the anterior pituitary hormone principle, genital growth was marked in fourteen. In two of them, aged 7 and 9 years, a condition appeared which resembled premature puberty, with the penis becoming as large as that of an adult. In the first case the testis was at the exterior ring, and suggested the possibility of a hernia. One year after injections were started and after the child had received 60,570 rat units, the testicle was in the upper scrotum. The boy was then operated on for strangulated hernia at which time the testis was placed in the scrotum. They added, "It is of interest that at 7 years he had a penis larger than that of his father and was having frequent erections." This seems to indicate that genital growth may occur without descent of the testis. They obtained descent of the testis in only 23 per cent of their cases.

Therefore, one may safely state that while anterior pituitary hormone substance should be administered to bring about descent of the testicle in children between the ages of 5 and 11 years, preferably early, it must be stopped short of producing abnormal genital growth. Occasionally one may find the hormone useful postoperatively to stimulate growth of an undersized testis or of one that is not growing. I met with success in one such case when I thought the testis was about to atrophy.

There are anatomical conditions that preclude satisfactory results from hormone therapy. I have demonstrated testes firmly fixed in the canal or on the external oblique aponeurosis that have required sharp dissection to free them from fixed tissue. Sometimes the testis was turned up on the fascia so that after it was liberated it was rotated to make a gain downward equal to that of its own length. Another condition which accounts for failures of hormonal treatment is the location of the testis in a congenital hernia. In my series 18 per cent had the testis in a hernial sac. When the presence of the undescended testis in a hernia can be demonstrated then injections are useless except to increase the size of the genitals. In such a case descent, if it did occur, would leave a hernia to be operated on unless the hormone closed the sac after the testis migrated. It is my practice in such cases to set a time for operation bearing in mind the child's age and the presence of any symptoms such as pain. If free from pain one may wait until the child reaches the age of ten years in a bilateral or eleven years in a unilateral case before proceeding with the operation.

Of the thirty-eight cases that I treated by the Keetley-Torek method thirty had hernias including the eight with the testicle in the sac. No instance was considered a case of hernia if the peritoneum was not exposed until brought into view by the dissection of the cord at the internal ring. Therefore, from anatomical point of view, in 82 per cent of my cases descent of the testicle or cure by injection therapy could not be expected.

If endocrine therapy fails what has operation to offer? The editorial in the American Medical Association Journal of January 22, 1938 quoted

the figures of Burdick and Coley in 1926 in which they found that only 50 per cent of 537 *orchiopexies* gave satisfactory results as to location and only 15 per cent as to size.

In 1933 Burdick and Coley reported that 123 out of 137 cases operated on by the Torek technic performed by several surgeons gave excellent results. Their failures were due to technical errors. Five testes sloughed, two because of infection and three because of tension; nine atrophied

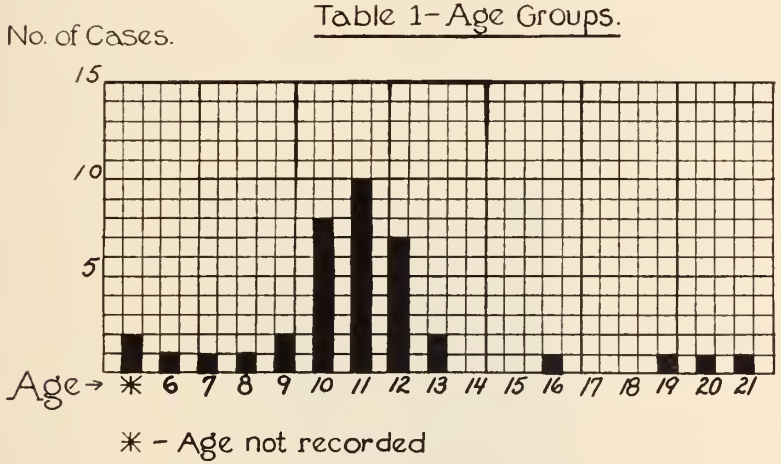

TABLE II

	KEETLEY-TOREK		BEVAN	
	Number of cases	Testis atrophied	Number of cases	Atrophy
Right	19	0	2	1
Left	10	2	1	1
Bilateral*	9	2	5	0
Total cases	38		8	
Total testes	44	4, or 9.9%	13	2, or 15.3%

* Only one side operated on in three cases.

because of too much tension. In spite of the fact that this was a composite series there were only ten per cent failures.

Myers reported 64 Torek operations on forty patients by four surgeons. He was able to follow up 34 of these and stated "we have yet to see our first failure."

In my series of thirty-eight cases, nine were bilateral, nineteen were right and ten were left sided making a total of forty-four testicles operated on by the Keetley-Torek method, because only one side was operated on in three of the bilateral cases. Four or 9 per cent of the testicles became atrophic.

Seven retracted to the midscrotum but are completely free and pendent. The remaining 33 testes are all free and low in the scrotum and normal in size. It has been noted that when a unilateral case was operated upon at advanced age the scrotal testis had already hypertrophied while the undescended remains always smaller but grows after being placed in the scrotum (fig. 1). Therefore, I cannot understand the statement of Meyer, who says the thirteen postpuberty cases that he followed up out of thirty-three, "in every instance the result has been as satisfactory as in the cases operated upon before puberty." To my mind it is necessary to operate before the scrotal testis has hypertrophied.

I have not been able to obtain descent by the use of anterior pituitary hormone. I find that the first thing that happens is the growth of the

FIG. 1. M. F. Keetley-Torek orchiopexy September 3, and December 26, 1930 at the age of 11 years. Photo taken April 11, 1939 shows right testis well developed, but smaller than the hypertrophied left.

penis and testes but, as a rule, not that of the scrotum. Hence I find it necessary to stop the injections in order to avoid overdeveloped genitals.

Torek developed his technic independently of Keetley but in 1905 he wrote, "The credit of having given us this new method, therefore, belongs to Keetley whose description of it antedates my first operation. Our methods differed not only in a number of details but even in some essential points."

Up to 1927 I made use of the modified Bevan operation for undescended testes. Since then I have become a complete convert to the Keetley-Torek operation which I believe should be used in nearly all cases. Keetley said, "I do not believe any surgeon practically acquainted with my plan would ever afterwards resort to any other." In the first place it gives the

lowest percentage of atrophies and secondly it guarantees a higher percentage of properly situated testes, even when the Keetley-Torek technique in which the gubernaculum instead of the testis is sutured to the thigh is followed. I had one case where the testicle retracted after the first stage and came to lie turned upward on the fascia of the external oblique aponeurosis. Therefore it is no wonder that testes may retract after the Bevan procedure.

Some hesitate to do the Keetley-Torek operation because it requires two steps in unilateral and three in bilateral cases. The second stage is a minor procedure and the children spend three days in the hospital.

As to the complaint that the child is handicapped by having a scrotum attached to the thigh, I wish to say that my patients are allowed to do anything a child convalescing from a hernioplasty would be permitted to do. In six patients the second stage was postponed for one year—in three because of illness, in one because of lack of funds, and in one because of indifference of the parents. A sixth was operated upon at the age of twenty on June 9, 1937. He has developed dementia praecox and cannot be approached for his second stage. Among Keetley's first series he reported a young man who after two years was satisfied to leave his testicle attached to the thigh and to do nothing more about it.

All that is required of the patient is to keep the channel clean between the scrotum and the thigh. There have been some complications in the hands of others, such as infection and loss of the testicle and rupture of the wound. I have had no such accidents and always obtained primary union at the first stage. Occasionally part of the flap of skin taken from the thigh at the second stage has sloughed but these have all healed rapidly by second intention without involving the testicle in any way.

The following case histories exemplify some of the points mentioned so far.

CASE REPORTS

Case 1. History. W. G. was a bilateral cryptorchid, aged 7 years. A first stage Keetley-Torek operation was performed on August 30, 1930 on the left side. This was followed on January 8, 1931 by the second stage on that side and a Bevan procedure on the right. Without cutting any vessels of the cord, the Bevan procedure was done because I was not satisfied that the left side would grow. In March, 1933 injections of anterior pituitary hormone were started; 6000 rat units were given in the course of eighteen months. By December, 1934 it was noted that the left testis was normal in size in the scrotum while the right testis which had retracted to the external ring had also grown to normal size. The child had grown two inches and gained fifteen pounds. Therefore, on July 8, 1935 I reoperated upon the right side by the Torek technique and found the testis lying upside down on the external aponeurosis above the external inguinal ring. The operation was entirely successful (fig. 2).

Conclusion. I believe that in this case the anterior pituitary substance aided growth of both testes and made the second operation of the right side possible.

Case 2. History. J. W., aged 8 years, was a small highly allergic boy and a bilateral cryptorchid whose brother was also a bilateral cryptorchid. He was fifty

and three-quarter inches tall and weighed fifty pounds on July 16, 1935. Both testes were in the canals and small. He had almost no scrotum (fig. 3a). He was given 2000 rat units of anterior pituitary hormone over a two month period; the same dosage was repeated in August, 1936. By July, 1937 he had grown two inches and gained fifteen pounds. His testes were now normal in size but had not descended

Fig. 2. W. G. Bilateral. First operation at the age of 7 years. April 30, 1930. Second stage January 8, 1931, also Bevan on right. 6000 rat units Antuitrin S. beginning March, 1933. Keetley-Torek operation, right side July 8 and December 21, 1935. Photo taken April 15, 1938. Note skin from thigh on bottom of scrotum.

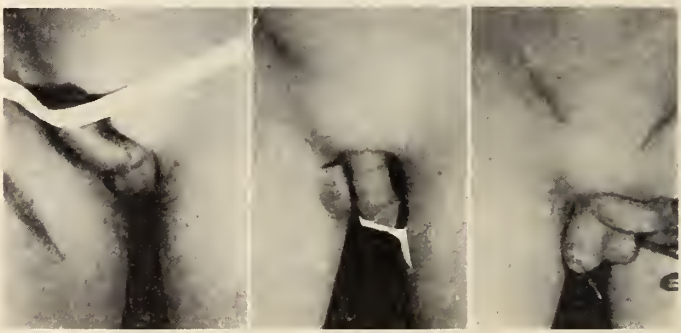

Fig. 3. J. W. Age 8 years. Bilateral.
A. (Left.) July 22, 1935, at beginning of hormone therapy.
B. (Center.) First stage performed July 23, 1937. Photo taken June 22, 1938.
C. (Right.) Both sides completed, December 24, 1938. Photo taken April 8, 1939.

and his scrotum had not enlarged. His penis was larger than usual for his age. Operation presented the problem of placing a good sized testis in a scrotum that barely existed. The first stage was done on the left side in July, 1937. The second operation was postponed at the request of his parents until June, 1938. During this interval the scrotum developed adequately. This was an example of how the scrotum can be enlarged with the Keetley-Torek technique by using a flap of skin

from the thigh. The last stage was completed in December, 1938 (fig. 3b) with excellent results.

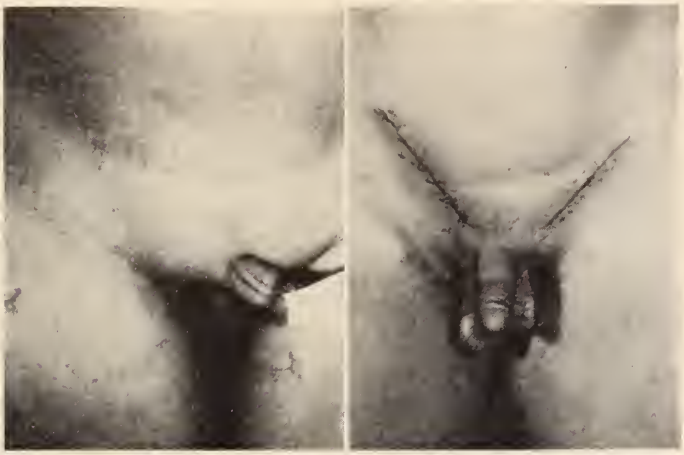

FIG. 4. I. M. Age 10 years. Bilateral. Keetley-Torek operations June 15, September 4 and December 21, 1936.
A. (Left.) Preoperative.
B. (Right.) One year and a half postoperatively.

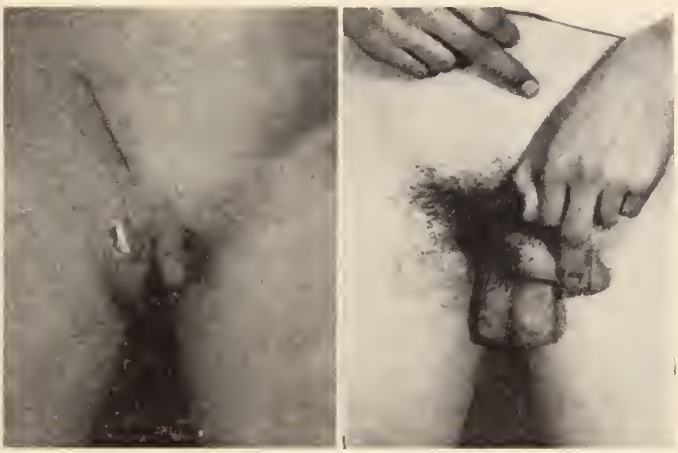

FIG. 5. D. S. Age 12 years. Bilateral. Operated elsewhere unsuccessfully, 1929; probably Bevan operation.
A. (Left.) Photo February 17, 1934 after first stage performed on December 15, 1933. Note old and new scars.
B. (Right.) Photo June 1938. Last operation July 17, 1934.

Case 3. History. I. M., aged 10 years, was a bilateral cryptorchid, whose parents refused a preoperative trial with hormonal therapy. Both testes were in the canal (fig. 4a). The three stages necessary were respectively done in June, September, and December, 1936. Because his testes were very small he was given 2000 rat units in July and August 1936. A definite increase in size resulted (fig. 4b). This is an example of the usual time required for the three steps.

Case 4. History. I had an unusual experience with E. C., aged 10 years, who was an epileptic bilateral cryptorchid. The gubernaculum was used to fasten the testes to the thigh as advocated by Keetley and by Wangensteen.

The first stage was performed on the left side in August, 1932. The second operation was done in August, 1933 using the gubernaculum to hold the testis to the thigh. A year later it was found necessary to repeat the procedure on the right side because the testis had retracted, to lie on the aponeurosis of the external oblique with the

FIG. 6. Perineal testis (right).
A. (Left.) Before operation, July 15, 1935.
B. (Right.) After operation, October 29, 1935.

FIG. 7. R. C. Age 12 years. Example of good result in unilateral case when done before hypertrophy of scrotal testis. Compare Fig. 1.
A. (Left.) Before operation, April 4, 1935.
B. (Right.) Photo July 29, 1936, one year after second stage.

lower pole uppermost and the gubernaculum stretching to the thigh. The final stage was done in December, 1934 with the testis still in good condition. In February, 1939 I examined him and found the right testis atrophic and free in the scrotum.

Case 5. History. One of the cases observed was an unsuccessful bilateral orchiopexy done by another surgeon in 1929 when the child was eight years old. I first saw the child in September, 1933. His testes were palpable at the upper edge of the pubis and under the inguinal scars. I performed the three steps of the Keetley-

Torek operation in December, 1933; April, 1934 and July, 1934. Photos show the good results obtained (fig. 5).

The perineal testicle is an ectopic testis that missed the entrance to the scrotum in its descent. Therefore, its position is not due to any endocrine imbalance or insufficiency nor to a shortened cord.

Case 6. History. In this instance an incision was made at the base of the scrotum just to the right of the penis (fig. 6). The testicle was freed from its perineal location by subcutaneous dissection and delivered. The cord emerged from the external inguinal ring in the usual manner and was of sufficient length. The right side of the scrotum was then entered and dilated sufficiently to hold the testicle. The testicle was placed in the scrotum and rested there without tension. The result was excellent.

DISCUSSION

There are several points about that technique which should be emphasized. 1) It is wiser to fasten the testis to the fascia. Care should be exercised not to include the epididymis in the stitch nor have the cord under tension. If tension results the gubernaculum should be employed. 2) At least half an inch of skin of the thigh on either side of the attached scrotum should be cut when replacing the testes into the scrotum. Very little fat should be left on the skin. Fine silk sutures are placed close to the edge, and good approximation is obtained without tension. The sutures are left in for at least one week. 3) The scrotal skin should not be undermined. 4) It is not necessary to suture the tunica vaginalis around the testis before suturing it to the thigh. 5) A Goodell uterine dilator was used to stretch the scrotum. 6) After the oblique incision in the scrotum is made, the ends of the opening are grasped with two forceps. The edge moist with blood is applied to the inner surface of the thigh making a red mark showing the site for the thigh incision. 7) At the end of the operation, one-quarter inch iodoform gauze is placed in the channel between the scrotum and thigh leaving it doubled so that a loop protrudes at one end. When it is time to change this gauze, after two or three days, a new double piece is placed through the looped end and the old piece is pulled through with the new piece. The new piece in turn has a looped end so that the procedure may be repeated. This is simpler and less disturbing than passing gauze with a probe or passing a hemostat to pull the gauze back. 8) After ten days the gauze is left out entirely and the child is instructed to clean the channel daily with alcohol on cotton applicators followed by talcum powder, always pressing against the groin and not against the scrotum suture line.

SUMMARY

1. The arguments favoring *laissez faire*, endocrine therapy or orchiopexy are considered; there is no good reason for the first.

2. Properly selected cryptorchids should be given a trial of hormone

therapy in the prepuberty stage. It has been used advantageously after operation. There are also harmful effects to be guarded against.

3. The selection of cases and therapy is discussed. Cases of spastic retention should be excluded.

4. Anatomical findings at operation show that about 80 per cent are accompanied by hernias which would not be closed by endocrine therapy.

5. Operative results and choice of operation are discussed; the author's choice is the Keetley-Torek operation.

6. Case reports demonstrate points to be observed in the surgical procedure and postoperative care.

7. Some new and special points in technic are presented, and pitfalls to be avoided are mentioned.

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SIGMUND FREUD: A CRITICAL APPRECIATION[1]

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In paying tribute to the memory of Sigmund Freud, the task of the neurologist differs in some measure from that of the psychiatrist in that the former is more organically minded and possibly more objective scientifically. To say that Freud was a great man or that he made important contributions is somewhat of a platitude which from the mouths of certain critics represents but an ill-concealed hostility. It is doubtful whether the time has yet arrived to permit objective criticism; and yet a certain degree of detachment is not altogether impossible. Like all great men, perhaps more than most, Freud has been both reviled and misunderstood in his own day. Many of his opponents did not actually read all his works, and those who did approached them with a bias which made sympathetic understanding extremely difficult. Others, who merely did lip service to psychoanalysis, did Freud an even greater injustice with their ambivalent praise. Many critics and some outright opponents appropriated much of what he contributed then proceeded to belabor him with his own weapons. But even greater injustice was done Freud by those of his followers who swallowed uncritically much that was scientifically indigestible. Many of the hypotheses and theories of Freud are not at all solid, and to accept all of them and defend them foolishly as facts of experience is to do violence not only to the greatness of the man but to much which promises to be of enduring worth. Some followers seemed to thrive on borrowed wisdom and donned a cloak of omniscience which did not altogether conceal the barren spaces beneath it. Since all *argumentum ad hominem* is generally fallacious, it is obviously unfair to judge Freud's contributions either by his opponents or by his followers.

It was Morton Prince, I believe, who first pointed out that psychoanalysis is not one thing, but that it consists of three fairly distinct parts. First, it is a body of psychology, that is, the psychology of emotivity or so-called dynamic psychology. In this it differs from physiological or academic psychology which dates back to Wundt, Lotze, Fechner, Helmholtz, James, Hall, Ribot, and a host of others. Second, it is a method of treatment or of therapy. Third, it is a method of investigation of human behavior, thought and emotion. One may, and one can, criticize psychoanalysis as a method of treatment, as a body of psychology, or as a method

[1] Memorial Lecture delivered at The Mount Sinai Hospital, New York, January 31, 1940.

of investigation, but it is important to bear the distinction in mind in order to avoid confusion. Psychoanalysis may be bad psychology and good therapy or good psychology and bad therapy. One may disagree with the doctrine of faith cures and concede that Lourde and St. Anne de Beaupré have yielded good therapeutic results. Each aspect of analysis may be criticized on its own merits, although it is true that in practice it is not easy to dissociate one from the other. This is particularly true of treatment and investigation.

One question which is legitimately raised is whether psychoanalysis is scientific. This question is not only valid but extremely important. But this reduces itself to the next question, namely, what is science? It is betraying no secrets to say that science as something concrete simply does not exist. Only those who are strangers to science worship it as a fetish. Actually science is nothing more or less than a well tested method. If one follows this method, the results may be regarded as scientific. Science consists of correct observation of phenomena or facts of experience, of repeatedly verifying those facts, of accurately gathering and correlating them, of drawing general conclusions, and of applying the deductions in other cases or to similar facts where the same conditions can be said to hold. If the conclusions are solidly based, they are called scientific. Provided one follows the scientific method, one may even set up theories which may later prove to be wrong. Strictly speaking one should always expect truthful results, but it is no secret that a good deal of nonsense may be the product of apparently scientific methods of investigation.

If we apply our question to the method used by Freud we must concede that it was scientific. He made observations, correlated them and drew conclusions. But Freud was also a poet of great imagination and intuitive wisdom. He had the capacity of drawing large conclusions from very small or even tiny observations. Very frequently he made a blind dive and came up with a pearl. Now this is a very dangerous method, and men with less skill and no vision may on blind diving come up with mud instead of a pearl. Very often one marveled at the great generalizations which Freud based on isolated observations. But it must be emphasized that such flights are fraught with error and that no wisdom or imagination can replace cumulative experience. To be a great scientist one must also be very much of a poet or at least have much ingenuity and wide imagination. These Freud possessed in large and dangerous measure. While there are innumerable people who do scientific work many are not great scientists because they do not possess ingenuity and imagination, because they lack wings. They are useful bricklayers but no architects, no creators.

Another widespread criticism that has been leveled against Freud is that he dealt too much with sex, and that sex is filthy. This is insulting to one's finest emotions no less than to one's intelligence. Only a filthy mind would

consider sex filthy. Obviously sex is as beautiful or as ugly as one makes it. Nor did Freud discover perversions. He certainly did not discover sex. The Greeks not only had a word for it, they had many words for it. The Romans too knew a thing or two about it. One needs only recall Marcus Apuleus. Bocaccio was not quite innocent either. The Marquis de Sade bequeathed a term and Sacher Masoch wrote novels on the subject. Krafft-Ebing also knew something of perversions, only he concealed them in Latin. But to call normal sex perverse is to expose oneself to justifiable suspicion. We all recognize the lady with an easy past who becomes virtuous when she can no longer sin and the impotent old roue who becomes a hounder of vice when he can no longer function as a rake. But suppose sex complexes are unhealthy, "filthy," then the thing to do is bring them out of the deep into the open and ventilate them. And this is what Freud did. Exactly what a surgeon does when he opens an abscess and lets foul pus come out. Surely no scientific person should bring a moral judgment to bear on facts. To do so out of place is not only to malign the investigators but the facts themselves.

Still another criticism which has been directed against Freud is that he set up a bad metapsychology. There is truth to this criticism. The word is a bad one. It means after or beyond psychology, which means nothing at all. The same applies to metaphysics. Psychology is not itself a science in the sense that physics, chemistry and mathematics are. At best it is an applied science. Introspective psychology is certainly not scientific. No more than transcendental reason is reason or anything that goes beyond physics or intelligence is either the one or the other. But Freud is entitled to his speculations, his theories and his hypotheses as much as anybody else, even though they may turn out to be wrong. The error of many of his followers is that they swallowed his hypotheses whole, anthropomorphized them, accepted them as facts and used them glibly as if they were concretely operative. Obviously this is nonsense.

A more pertinent criticism is that many psychoanalytic facts or observations need interpretation. This may lead to grave fallacies. Actually science seeks to avoid interpretation as much as possible, just as it seeks to avoid variables or to account for them. One tries to avoid interposing anything between a proposition and its conclusion. In the proposition two and two make four, one interprets nothing and interposes nothing. One fact follows from another. Unfortunately all psychology is compelled to use variables and to try interpretations. This is a real inherent difficulty. We are dealing with the most complex aspect of human knowledge and we know so little about it. We do not know what an idea actually is or how we think. We believe that we use the brain in the process of thinking, although one would hardly suspect the fact from the way many people think nowadays. Maybe some day we shall know

what an idea actually is, and maybe we shall be able to speak of thinking in terms of physics and chemistry. For the present we must be content with language, with interpretations of behavior, with introspection and with verbalization of ideas. The difficulty, as all great writers know, is that words are seductive. It is not an uncommon experience for a writer to put his ideas into words only to find that when he finished the sentence it has not actually expressed what he thought. Many persons write better than they think. There is even danger that beautiful writing will succeed in concealing bad thinking. That danger or that weakness exists in Freud as it does in other great poets and writers. It is no accident that Freud received the Goethe prize. One simply has to recognize that seductive language itself can do violence not only to ideas but to facts of observation. Let us hope that some day we shall be able to speak in more scientific language. For the present one must constantly bear these criticisms in mind in the interest of clear thinking and scientific conclusions.

We come now to the contributions which have permanent value, which I believe have become part of the heritage of human knowledge. The first is Freud's conception of the unconscious. This differs entirely from all previous conceptions of Schopenhauer, von Hartmann, Ribot, Janet, Prince and others. Freud conceived of an active, dynamic unconscious which is entirely outside the realm of awareness and which is capable of influencing indirectly conscious behavior. This, it seems to me, is his great contribution. He has made possible the understanding of motives and of inexplicable or so-called queer behavior. It is all very well for Adler to speak nonsense in his own way and for Jung to speak of a universal unconscious, but they have no right to call it psychoanalysis. Only if one accepts Freud's conception of the unconscious can one speak psychoanalytically. To give it any other twist is to think not only erroneously, but, I believe, also not honestly.

If one accepts Freud's view, a number of practical and theoretical conclusions naturally follow. The first is that there can be unconscious conflict. This, again, differs from conscious conflict with our environment which we all have and which may be consciously resolved on its merits. The unconscious conflict is not capable of such easy solution, at least not until it is brought to the surface and worked out. Repression, too, is an unconscious process and differs entirely from suppression which is a conscious, purposive exclusion of ideas from the field of awareness. The two words are used interchangeably, erroneously it seems to me, by those who do lip service to the ideas of Freud. Many of those who have an ambivalent attitute to Freud, consciously or unconsciously use and misuse many of his ideas, then berate him for refusing to reject that which their own resistance forbids them to accept.

A more disputed concept is that of the emotion which gives tone to ideas, which according to Freud motivates the behavior of individuals as well as

of groups. I refer to his concept of the libido which he regarded as rooted in primitive sex impulses. Unfortunately the word libido is linked in language and in some minds with libidinous or lecherous ideas. Again ugly sex rearing its ugly head. Well, each one to his taste. Primitive sex emotion can be beautiful and to love deeply is an art. To love deeply is to live. Any fool can make a child, but only a poet can make love. What Freud has shown is that the sex impulses, however primitive they may be, begin to operate early in childhood. Of course, they are not the same impulses in the child as they are in the adult. They are crude, inchoate, inarticulate, and unripe, but they are there, and not to see them is to close one's eyes to simple facts of observation. Already at the age of two or three, one can see differences of behavior according to sex. The little boy will pick out a baseball bat and the little girl a doll. One need not be a very great observer to realize the difference of attitude of the little boy or girl to the parent of the opposite sex. All the sex instincts are rooted in early life, only the expression of the impulses is delayed until maturity. In most individuals they grow normally, in some they get twisted and become the source of neuroses later in life. Minerva may have sprung full-grown from the head of Zeus, but the sex instincts do not suddenly appear from nowhere at puberty.

When we come to the question of symbolism we touch admittedly on what is the weakest link in psychoanalysis. Certainly the interpretation of symbols permits of the wildest flights of fancy. But there were symbols and interpretation of symbols long before Freud. In any case, they are not the most important part of psychoanalysis. An example, however, of the misuse of symbols by critics is the twist Adler gave to the castration complex. The scientist may frankly reject this symbolic concept. What did Adler do? He castrated it, took the sex glands out of it, made it respectable, and called it an inferiority complex with which he explained everything from war to epidemics.

The statement has been made that Freud did away with inhibitions. The very opposite is true. He did away with prudery and not inhibitions. To inhibit is almost the first lesson in life one has to learn. One cannot become a social being unless one constantly inhibits antisocial or unethical behavior, and it is foolish to say that Freud encouraged antisocial activities. As a matter of fact we are compelled, if we wish to survive, constantly to build inhibitions from the eyebrows up in order to control impulses from the eyebrows down.

One of the finest concepts that Freud has evolved is that of sublimation, which may be defined as the gratification of primitive, socially-tabooed impulses in ways which are socially acceptable. This has been assailed on the ground that it does violence to ethical principles and noble ideals to allege that they are rooted in ugly unconscious impulses. The argument is not altogether convincing, and does not frighten or upset the mature

adult mind. Friendship is a beautiful sentiment even though it be alleged that it is the sublimated result of unconscious infantile homosexuality. The rose is no less fragrant because its roots are nourished by manure. What is important is the capacity for the sublimation of impulses into ideals and socially useful ends. The beautiful poem written by the ardent lover is no less beautiful for its sublimation of a primitive sexual urge.

A very great contribution of Freud is his emphasis on the dignity and worth of man. His whole psychology revolves about the struggles and conflicts which the individual goes through in the process of development. Contrary to popular as well as to academic misconceptions Freud has emphasized the need for strength of the individual in his conflict with social forces. Society seeks to subdue the individual and mold him to its needs, whereas the individual constantly wants to express his own individuality by throwing off restraints. This conflict is shown to be operating at all times, and has been from time immemorial. The fiction of a state has been set up to enslave and destroy the individual. Actually there is no state unless there be individuals to give it form. Destroy the individual and you destroy the state. The intensity of one's individuality is gauged by his ability and his propensity to rebel against social forces and the index of one's sociability is measured by his capacity to curb his individuality to meet social needs. He who cannot express the one becomes an undifferentiated cog, and he who cannot meet the other becomes a disruptive element. Freud has shown the nature of the conflicts one must go through in the process of attaining both sociability and individuality. It is well to bear this in mind in these days when the individual is assailed by false social philosophies and threatened with destruction by the ruthlessness of a fetishistic and malignant concept of state.

More important even than the emphasis on the psychology of the individual is Freud's contribution of the concept of rationalization. It has focused attention on certain types of thinking which pass for intelligence and stripped the pretense from much of the cant which parades as reason. Rationalization is the process of self-deception by means of false but plausible reasoning. Frequently the individual is employing it without being aware of the underlying mechanism of thought and motive, and insofar as he is unconscious of the process, he cannot be regarded as a hypocrite. But the line between this and the conscious purposive deception known as hypocrisy is very thin, and it is frequently difficult to tell where rationalization ends and hypocrisy begins. Incidentally the definition of rationalization may be applied with slight modification to much which passes for philosophy, psychology, and metaphysics.

Psychiatry has been accused by uninformed critics of being a verbal discipline. This is not true, of course, although there is some justification for it. Actually psychiatry is as rooted in medicine as any other specialty. The brain, though complex and difficult to know, is the organ of

thought. There is evidence of a very strong trend of psychiatry toward more physiology, physics, chemistry and medicine in general. It is no prophetic folly to predict that much which passes for modern psychology and psychiatry will turn out to be plain gibberish. But language is the tool of normal and abnormal thinking. To this language Freud has contributed enormously, indeed he created a rich vocabulary, almost a whole language which enables the psychiatrist to express his ideas more fluently and intelligently at the same time that it enables the patient to grasp the meaning of his vague symptoms in more precise terms. Every neurologist and psychiatrist knows how hard it is to convey ideas and shades of meanings to patients, how easily patients misunderstand what is said to them and how frequently they misinterpret words. Up to the advent of Freudian dynamic psychology, classificatory psychiatry had almost reached a blind alley. If Freud did nothing else but contribute a rich language, psychiatry would have reason to be very grateful.

But Freud has also enriched with his language other branches of learning. In addition to fructifying psychology and psychiatry, he also enriched education, sociology, anthropology and literature. One is almost tempted to say that there is hardly a field of human thought where language plays a role which has not felt the impact of Freud's psychology. Depending upon whether one is for or against Freudianism, one may rejoice in the fact or deplore it, but one cannot escape the conclusion by shutting his eyes to it.

This is not the place to review Freud's great contribution as a neurologist, before he devoted his life's work to analysis, to the study of what are known as cerebral birth palsies and to the language disturbances which go by the name of aphasia. I may even mention his original discovery of the anesthetic effect of cocaine, although Koller justly received the credit for the subsequent researches which made it available in human surgery.

In conclusion, it is difficult to appraise the worth of Freud's contribution, to say what is of permanent value and what is ephemeral, or what is likely to remain as the heritage of human knowledge and what will yield to the corrosive effect of time. If I should dare to become a fool and a prophet, I would say that psychoanalysis will not survive best as a method of treatment, despite the acknowledgment that certain neuroses are best treated by it. I would venture the guess that analysis will be remembered longest for the insight into normal and abnormal behavior which it has vouchsafed and for its excellence as a method of investigation. I am not so sure that it will survive as a body of psychology, although one can only feel grateful for its honest approach to the study of sex instincts. But if one cannot predict how long Freud's contributions will be remembered or how much of them will survive, one can state with assurance that no man of his generation has had wider influence or stamped his personality more deeply on the thinking of his age.

NOTES ON HEMOPTYSIS

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Of the symptoms which arise during the course of thoracic diseases, hemoptysis is the one most apt to arrest the attention of the patient. It has for him an ominous import, bringing with it the threat of serious or even fatal disease. Yet hemoptysis is of itself rarely threatening to life, and many of its causes, while serious, are susceptible to cure. If we except putrid lung abscess, in which fatal hemorrhage is not an exceptional occurrence, rupture of an aortic aneurysm into a bronchus, and advanced ulcerative tuberculosis, we may be assured that even large hemoptyses very rarely have a fatal issue.

When we speculate on the various causes of the spitting of blood it is well to remember that the lungs lie at the crossroads of the circulation where morbid conditions originating elsewhere in the body may for the first time and even exclusively manifest themselves. How often is the spitting of blood the first sign of a pulmonary embolization due to a concealed phlebitis, of all hemoptyses the only one accompanied by pain? Everyone has had the experience with the large repeated hemoptysis of a latent mitral stenosis. Who has not encountered the bleeding from a metastatic tumor in the lung when the primary growth, often in the kidney, gave no inkling of its existence?

It will be noted that these are all instances of hemoptysis the source of which is the pulmonary vessels. If, however, we view the lung only as an organ in which venous blood passes to and from the heart, we are apt to have an imperfect understanding of the causes of hemoptysis. The bronchi are also a part of the respiratory organ, with a separate blood supply derived from the aorta through the bronchial artery. Obviously, branches of the bronchial artery may bleed as well as the pulmonary vessels and for this reason it would be an oversight when we are investigating the spitting of blood to omit consideration of pathological conditions in the bronchi.

In the era which preceded the use of the roentgen ray the distinction between bleeding of pulmonary and of bronchial origin was a difficult one to make. There can be no doubt that many cases of bronchial bleeding were wrongly attributed to disease of the lungs. In those days everyone who spat blood was under suspicion of being tuberculous, a suspicion which was often based on dubious physical signs. I well remember with what authority the presence of tuberculosis was asserted by eminent clinicians because a few râles were heard at the apices of the lungs. Happily, the

roentgen ray has freed us from the tyranny of outmoded physical diagnosis. We can now have the assurance that a lung which is normal according to modern standards of roentgen technique and interpretation, is free of tuberculosis. We may be confident in assuming, in such a case, that the spitting of blood has some other cause than pulmonary tuberculosis.

Now it happens that in numerous cases of hemoptysis the roentgen film reveals a completely normal lung. In the absence of any obvious pulmonary disease it is at once pertinent to inquire whether the blood may not have come from some lesion in the bronchi. The answer to this query is of practical importance because in some instances it leads directly to curative treatment.

My interest in the subject of bronchial bleeding was born in the early days of pulmonary roentgenology at The Mount Sinai Hospital. Since then a considerable number of patients who presented an interesting story were admitted to the wards of the hospital.

Usually without warning, either by pain or cough, the patient became aware of a salty taste in the mouth which was followed by a profuse spitting of liquid blood. Sometimes this was the initial experience; in other cases the bleeding had recurred for a number of years. Usually the bleeding stopped within a few days with no harmful effect on the patient's health. Rarely it was alarming and was repeated in large amounts. We were not long in doubt as to the approximate diagnosis. Pulmonary disease, thanks to the roentgen ray, could be ruled out; bronchoscopic examination likewise informed us that there was no visible lesion such as a tumor in the bronchus. The blood must, therefore, have issued from a vessel in the bronchial mucosa. It need hardly be added that in all cases the precaution was taken to rule out any disease of the blood-forming organs or any systemic disease of the blood vessels.

For want of a better term we designated this malady "benign" or "essential" hemoptysis to indicate its essentially harmless character and also the fact that it is not associated with any gross pulmonary or bronchial disease. Of course, this disease has long been known to clinicians although its significance has not, in my opinion, been recognized. English physicians in the middle of the last century spoke of certain cases of hemoptysis as "gouty" or "arthritic". It will do them no injustice to assume that this designation reflected the prevailing tendency to ascribe obscure symptoms to arthritis or gout. Perhaps some of these cases were instances of the condition described here. Others may have been due to arterial hypertension which occasionally induces large hemoptyses. As to this, their records tell us nothing; little was then known of high blood pressure and the sphygmomanometer had not yet been devised. Somewhat similar cases which showed a familiar trend were recorded by Ottenberg and Libman from The Mount Sinai Hospital. In a few of the cases the hemoptysis occurred at or before the menstrual period and in one patient

it so recurred regularly for years. It would take us far afield to discuss the implications of such cases but they raise a doubt as to the existence of a true vicarious menstruation. May we not rather assume that in cases of so-called vicarious bleeding there is associated some vascular lesion in the bronchial tree such as must exist in cases of essential hemoptysis?

What is the cause of essential hemoptysis? I have often heard it suggested that the bleeding is caused by the rupture of a varicose vessel in a large bronchus. However, it is easy to convince oneself that this is not the case. With few exceptions, these patients were bronchoscoped, often when they were actively bleeding, but no varix could be seen in any bronchus of a size which would permit the entrance of a bronchoscope. Nor was a bleeding point of any kind ever visible. There is every reason to believe that the blood comes from the mucosa of one of the smaller bronchi and that it results from the erosion of a very small vessel. As to the nature of the process which causes this erosion, we have no knowledge. Perhaps the process is similar to the one which elsewhere causes an epistaxis or to the hemorrhagic erosions of the stomach. It has seemed to me that capillary emboli or thromboses which play a role in the production of focal necrosis elsewhere in the body may, in a susceptible tissue such as the bronchial mucosa, induce an ulceration of small vessels. Compared with other mucous membranes such as in the mouth or nose, that of the bronchi exhibits an excessive friability. The bronchoscopist will testify to the ease with which the bronchial mucosa can be made to bleed under the slightest trauma.

Essential hemoptysis represents the simplest, I might say the purest form of bronchial bleeding, in the sense that we observe no gross pathological change in connection with it. In all other instances of bronchial hemorrhage we may assume the existence of some morbid condition in the bronchus which can usually be discovered by diligent search. One of the most interesting and practically important of these is adenoma of the bronchus. This disease was for the first time systematically studied at The Mount Sinai Hospital where a considerable number of cases was observed and followed for many years.

The bleeding in cases of adenoma of the bronchus is, in general, similar to that in essential hemoptysis. It is usually profuse, which is explained by the vascular nature of the tumor. From its exposed postition at the orifice of a main bronchus, it is subject to repeated trauma and infection and, therefore, the bleeding may be expected to recur frequently. Many of the cases bled intermittently for years and in one case the hemorrhages began thirty years before. A characteristic feature of the bleeding is determined by the position of the tumor at the entrance of a main bronchus which it occludes. For this reason the expectoration of blood follows promptly on the hemorrhage so that there is less tendency for the blood

to overflow into the bronchial tree. I have been struck with the fact that in a number of the cases the bleeding ceased as abruptly as it began and that it was not succeeded by the spitting of dark blood or clots. This would indicate that the blood neither was aspirated into the smaller bronchi nor did it come from some disease in the depths of the lung. This phenomenon at times makes it possible to diagnose adenoma from the history alone. Although profuse hemoptysis is the most dramatic symptom of adenoma, the latter condition is more often brought to our attention by the more prosaic infections of the lungs, bronchi and pleura which follow in the wake of the bronchial obstruction which it induces.

No discussion of the hemorrhages due to foreign bronchial bodies would be complete without some consideration of the calcareous deposits known as broncholiths. It may be questioned whether all concretions of this type are the stony nuclei of tuberculous lymph nodes. In any event, my experience with them as a cause of hemoptysis has led me to regard them as a by-product of the tuberculous infection. The more frequent use of the bronchoscope has led to a recognition of the occasional relationship of caseous-calcareous bronchial lymph nodes to bronchial hemorrhage, and a new clinical complex is taking its place in the larger framework of pulmonary tuberculosis. As a cause of repeated, often profuse hemoptyses lasting in cases over a period of years, tuberculous lymph nodes must be given a definite place. As a rule the nodes are situated in close contact with one of the major bronchi which they compress and gradually invade. The caseous-calcareous mass may erode a fairly large bronchial vessel and thus induce nearly exsanguinating hemorrhages. Under these conditions calcareous material may be extruded and expectorated. At times it may even be seen through the bronchoscope. Unfortunately, the clinical diagnosis cannot rely too much on the spitting of lung stones, which seems to be an uncommon event. We may console ourselves with the knowledge that tuberculous nodes which cause hemorrhage also cause a stricture of the bronchus with corresponding physical signs and pulmonary changes. In regard to the roentgenologic interpretation of calcified lymph nodes in cases of bleeding, one has to exercise some caution. The shadows of calcareous nodes are so frequently seen on roentgen films that it would be altogether irrational in most cases to see any relation between them and hemoptysis. Only large lymph nodes which visibly cause a distortion or narrowing of the bronchial lumen can have any great significance.

The association of hemorrhage due to tuberculous lymph nodes and pulmonary tuberculosis is an inconstant one. I have often observed cases of repeated hemoptysis due to large lymph nodes without any evidence of tuberculosis in the lungs. On the other hand this condition may accompany pulmonary tuberculosis in various stages of activity or healing. It is especially arresting to find patients who have apparently healed fibroid tuberculosis yet have frequent large bleedings. In such cases when, in

addition, a rhonchus is audible over a large bronchus, I have rarely been disappointed in the search for a caseous or calcified lymph node pressing on a major bronchus. Like other foreign bodies, in exceptional instances the calcareous deposit may be situated in a second or third order bronchus. I am reminded of a young woman who for several years had large hemoptyses who finally expectorated a broncholith with a cessation of the bleeding. The roentgen film showed the concretion in the periphery of the lung.

Foreign bodies of various kinds introduced from without are not infrequent causes of hemoptysis. It is understandable how such a body, which has lodged in or near a bronchus, will give rise to ulceration and, therefore, to the repeated expectoration of blood. This is so well recognized that failure to bronchoscope such patients must be considered a cardinal oversight. Although it is usually the case, such a foreign body need not lie in a main bronchus. I recall a man who had been bleeding profusely for years after a gunshot wound of the lung. Under the guidance of the roentgen film Dr. Lilienthal removed the bullet which lay near the surface of the lung.

The hemorrhages which occur with pulmonary cystic disease and suppurative bronchiectasis are often profuse and probably have a similar pathologic basis. In both these conditions, submucosal ectasia of blood vessels in the bronchial walls are prone to rupture with alarming hemorrhages. The occurrence of hemorrhages in so-called dry bronchiectasis is more puzzling to the clinician because the absence of cough and purulent expectoration which previously have given no hint that the patient had any bronchial disease. For this reason one should not omit a graphic study of the bronchi in any case of excessive bleeding when the clinical examination reveals no pulmonary or bronchial disease. Only recently I observed a young woman who was totally incapacitated over a period of six years by frequently repeated, enormous hemorrhages. The discovery of extensive bronchial dilatations of a lower lobe was wholly unexpected as she had neither coughed nor produced any sputum.

In conclusion, it may be in order to set down a few observations on the bleeding in pulmonary tuberculosis. As is well known, tuberculous hemoptysis is usually not serious or very profuse except in the terminal ulcerative stages of the disease when large vessels may be exposed in cavities and rupture. Perhaps not as well known is the fact that hemoptysis is more common in the relatively benign chronic forms of the disease. There is nothing more disquieting than the frequent small bleedings, often no more than streaking, which disturb the peace of mind of a patient who has a fibroid tuberculosis of the apices or upper lobes. The patient may have been enjoying good health and have had every reason for believing that his disease was completely arrested. The roentgen film contributes to this feeling of security as it often shows nothing more than a bilateral

area of fibrosis with no indications of activation of the disease. A close inspection of the film, however, often discloses tiny areas of transparency, especially at the extreme apices, which are doubtless small cavities or bronchial dilatations. Furthermore, if the sputum is examined frequently enough it may be found that the patients are at odd times discharging tubercle bacilli or that they are swallowing them. We have come to regard this type of tuberculosis as hematogenous in origin. The apparently benign fibroid lesion I have described develops insidiously, over a period of years, from an initial miliary tuberculosis of the upper lobes. Moreover, the hemoptysis which occasionally signalizes the clinical onset of tuberculosis is very apt to be based on such a fibroid lesion which has in fact been in existence for some time in a latent form, rather than on an exudative tuberculosis.

One can regard these repeated though small bleedings as serious merely in their implications. They indicate that the tuberculous process is still in being and that it is still capable of spreading the disease. As in so many other instances of hemoptysis which I have presented, it seems altogether likely that here also we have a form of bleeding, the origin of which is in the smaller bronchi rather than in the lung itself. It gives emphasis to the belief that any form of hemoptysis which is frequently repeated, or recurs over a prolonged period, is of bronchial derivation.

HEMATOMETRA AND HEMATOSALPINX IN A BICORNATE UTERUS IN A PATIENT WITH A SOLITARY KIDNEY

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The following case is presented because of its rarity and to emphasize the association of genital and urinary anomalies.

CASE REPORT

History. V. M., a 15 year old girl whose previous medical history was essentially negative was admitted to the Gynecological Service of Dr. I. C. Rubin, on October 31, 1937, because of severe cramp-like lower abdominal pains of 24 hours' duration. The pains were intermittent at first but after 24 hours became constant and localized in the right lower quadrant. There was neither nausea nor vomiting. There was no vaginal bleeding. The menses, which had begun a few months before, were regular but accompanied by severe dysmenorrhea for the first two days. The dysmenorrheal pains were experienced low in the abdomen and on both sides. The last menstrual period occurred on October 15.

Examination. There was a normal introitus which permitted a one finger examination. The cervix was pushed to the left side of the vagina. In the right half of the pelvis was a fixed, slightly tender mass, about 3 inches in diameter. An irregular, firm, fixed mass could be palpated behind the cervix and to the left in the posterior fornix. The temperature on admission was 100°F.

Laboratory Data. The urine examination was negative. The hemoglobin was 90 per cent; white blood count 10,500, differential 80 per cent polymorphonuclear leucocytes (non-segmented forms 4); lymphocytes 18 per cent, monocytes 2 per cent. Sedimentation time was normal, 1 hour, 10 minutes. The blood pressure was 135 systolic and 80 diastolic.

Course. The provisional diagnosis was bilateral ovarian tumors, probably dermoids, with the possibility that the right dermoid cyst was twisted. Operation was, therefore, advised and a laparotomy performed under gas, oxygen, ether anesthesia.

Operation and Findings. On opening the abdominal cavity about 20 cc. of free and clotted blood were seen. The greater omentum was adherent to a large conglomerate mass occupying the right half of the pelvis. On the left side of the pelvis was an organ which appeared to be a normal uterus, to which was attached on its left side a normal tube and ovary, and a single round ligament. This uterus and its adnexa were found lying in the cul-de-sac. To the right of these structures was a mass which proved to be a huge dilated hematosalpinx 8 inches in length and 2 inches in diameter. This tube was intimately adherent to the right ovary which was firmly adherent to the omentum and pelvic peritoneum but was otherwise normal. The tube sprang from the right side of a cystic mass which measured 6 inches by 3 inches, and resembled a gravid uterus of three months (fig. 1). During the operation, digital examination of the vagina verified the presence of one cervix which apparently communicated with the uterus on the left side. It was then decided that the right cystic mass was a rudimentary uterus with a hematometra due to a blind cervical end caused by the absence of the cervix. Between the two uteri and running

posteriorly to the rectosigmoid mesentery was a band represented in figure 1. This was interpreted as the recto-vesical ligament. There was no communication between the right and left uteri which were separated and only connected by ligamentous bands of tissue between the two fundi. A right round ligament was present. There was no malrotation of the intestine and the cecum occupied its normal position.

The greater omentum was separated from the mass on the right side. The right infundiculo-pelvic and round ligaments were ligated and cut. The right distended tube and right ovary were then removed. The rudimentary uterine horn, filled with blood, was freed and extirpated. Despite extensive exposure of the pelvic floor, no ureter could be identified. The pelvic floor was completely peritonealized.

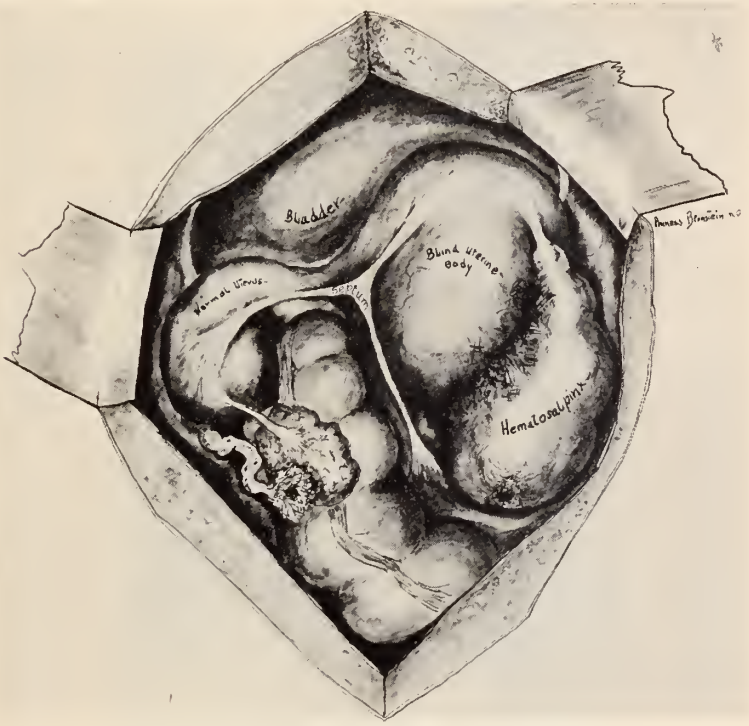

FIG. 1. Laparotomy findings: two uteri with the distended right uterine body and the right hematosalpinx

The abdominal wall was closed in layers in the usual manner with three silk stay sutures through fascia and skin, and pincettes for the skin.

The report of the pathologist read as follows: Specimen consists of a congenital abnormality related to an unfused upper end of the Mullerian ducts. At the time of operation, there was found a uterine body with the left adnexa. This uterus was in communication with the cervix and vagina. The entire specimen found on the right side was a pear-shaped organ resembling a uterus. This presented an enlarged and dilated tube filled with old blood. Adherent to it by dense adhesions was a slightly enlarged ovary.

The uterine body removed measured 10 x 7 x 4.5 cm. There was an enclosed sac (fig. 2) without any communication with the main uterus, cervix or vagina. At operation the uterine cavity contained 150 cc. of black, tarry blood. The serosa on

one aspect was smooth; on the other half, however, there were numerous rather dense adhesions. When this uterus was opened, the myometrium appeared rather pale, homogeneous and 1.5 cm. in thickness. The inner lining showed suggestive endometrial mucosa which was congested toward one end and brown in color toward the other.

The Fallopian tube was elongated to 12 cm. dilated in retort shape fashion and covered by numerous dense adhesions. Near the outer pole there were several cystic structures containing old blood. A small opening into this dilated hematosalpinx revealed the presence of old blood within it.

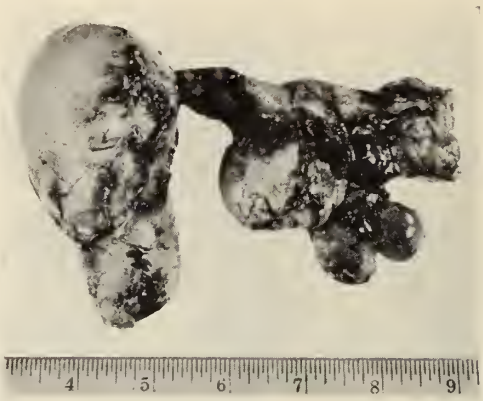

FIG. 2. Specimen of the distended right uterus and its dilated tube

FIG. 3. Specimen of the right uterus showing dilated endometrial cavity and ovary adherent to the tube

The ovary was slightly enlarged, somewhat cystic, covered by adhesions between it and the tube. It measured 5.5 x 4 x 2 cm. (fig. 3).

The pathological diagnosis was: hematometra of a rudimentary cornu in a uterus bicornis; hematosalpinx.

Postoperative Course. The patient made an uneventful recovery and was discharged on the fifteenth day with the following note: The wound healed by primary union. The pelvic examination revealed a cervix continuous with the uterus on the left side. There was a firm exudate in the region of the right fornix.

Since we were unable to identify the right ureter an intravenous pyelogram was performed before the patient left the hospital. The report was as follows: There

is no visualization of the upper right urinary tract. The left kidney is extremely dilated. The calyces show relatively little clubbing, however. The ureter is normal in calibre; the change from dilated pelvis to normal ureter taking place probably at the utero-pelvic junction (fig. 4).

The patient was studied by the urologists who found normal urine, normal phenol-sulphonephthalein excretion and normal blood chemistry. Culture of the urine proved to be sterile. The blood pressure remained normal, 126 systolic and 78 diastolic. The cystoscopic examination showed normal left ureteral orifice with good indigo-carmine excretion from this side. No orifice could be visualized on the right side. It was apparent that on the right side there was an absence of the kidney and ureter, while on the left side there was a non-obstructive hydronephrosis. For the latter condition, no operative interference was indicated.

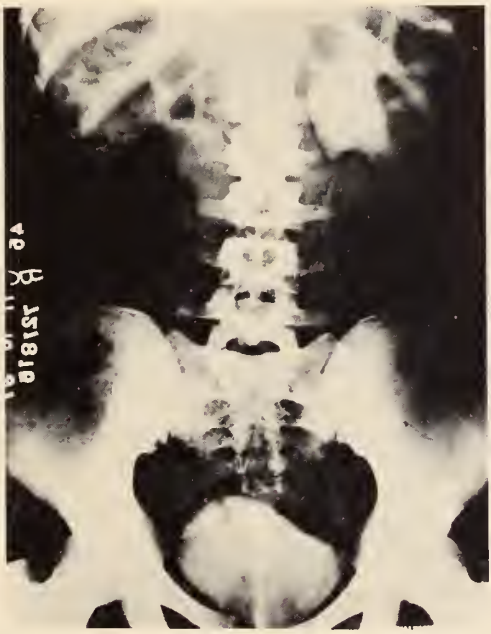

FIG. 4. Intravenous urogram showing absence of the right kidney and hydronephrosis of the left kidney.

Subsequent Course. The patient has been under constant observation for over two years. There have been some episodes of left loin pain during this time but the symptoms subside spontaneously. An intravenous pyelogram on January 27, 1940 showed similar findings to those 26 months before. She was last seen on February 3, 1940 at which time she had no complaints, her menstrual periods were regular and without any dysmenorrhea.

COMMENT

The association of congenital anomalies of the genital and urinary tracts has been noted for a long time. Ballowitz (1) in 1895, collected 213 cases of congenital solitary kidney and found 73 genital malformations in 103 of the cases where the genitals were examined. In 1932 Collins (2) re-

viewed 581 cases of unilateral kidney and found genital defects in over fifty per cent. Malformations of the genital tract according to Macalpine (3) occur more frequently in cases of solitary kidney than with any of the other renal dysplasias. Ballowitz and Collins (1, 2) both found a preponderance of genital defects in females. Lillard (4) attributes to Paltouf the statement that in almost 50 per cent of uterine malformations, some type of developmental renal disturbance is found. Rubin (5) has also pointed out that anomalies of the urological tract may simulate genital lesions. Among the more prevalent malformations found in the female with unilateral renal aplasia are bicornate uterus, uterus didelphys, double vagina, and absence of the uterus or vagina.

The incidence of unilateral kidney, according to Beer and Hyman (6) is 0.5 per cent. They mention a series of 136,766 autopsies in which 180 cases of solitary kidney were found. Ball and Evans (7) found a single kidney three times in 2000 autopsies at St. Bartholomew's Hospital, London. It has been noted that anomalies of the genital tract, especially uterus didelphys or bicornate uterus, with rudimentary horn are also comparatively uncommon. The occurrence of two such malformations is very infrequent.

The etiological factor responsible for the association of these anomalies of the genital and urinary tracts is found in their close embryological development. Partial fusion of the Mullerian ducts account for the production of the uterus bicornis with its rudimentary horn. The hematometra and subsequently the hematosalpinx developed because this partial fusion resulted in no communication between the cavity of the rudimentary horn and the cervix and vagina.

It is advisable, therefore, in all cases of anomalies of the genital tract to investigate the urinary organs.

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BRONCHIAL ASTHMA AND GALL BLADDER DISEASE

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The causes of true bronchial asthma are so numerous that to discover the actual etiological factor in a particular case often taxes the ingenuity of the most careful clinical investigator. Even when the cause of the attacks is determined, it is not always certain that a cure can be effected by a rational course of treatment. So many psychogenic factors develop in those who have had the disease for a long time that the threshold of stimulation becomes lower and lower and the patient may be thrown into a spasmodic attack for a reason not immediately apparent to the observer. One attack may lead to another in an almost rhythmic procession, with the result that in a severe case the patient is rarely free from the fear of his disability. In fact this constant apprehension frequently becomes the starting point for a new attack after one has just subsided; so that in handling these patients the problem often becomes as much a psychological one as a purely physical one.

One group of cases with bronchial asthma exhibit, in addition, concomitant abdominal symptoms which tests may indicate to be the result of a food allergy that brings about not only bronchial spasm but also abdominal discomfort of a varied nature. In some, these manifestations are confined to the right upper quadrant of the abdomen, and this has been designated as the gall bladder type of asthma. These patients may have symptoms that persist for many years. They are always short of breath, have sleepless nights with dyspnea and cyanosis and complain of constant indigestion and discomfort in the upper abdomen, with gaseous and biliary eructations after meals. They are apt to be well-nourished, or even obese and plethoric. A study of the biliary tract may reveal no evidence of abnormal function and no stones may be visualized, yet certain foods which need not necessarily be fatty in nature cannot be taken without initiating either an asthmatic or a so-called gall bladder attack, or both.

When operation upon patients with asthma and this train of chronic gall bladder symptoms reveals no disease of the gall bladder or the ducts, the conclusion is that they have a type of hepatic allergy, with edema or cloudy swelling of the liver causing the right upper quadrant attacks (1). Nevertheless, allergic reactions in the gall bladder or ducts, or in the liver itself, may, after a time, result in a superimposition of infection. Consequently, definite gross pathology, discovered at operation, may be secondary to a long standing allergy.

On the other hand, there are cases with primary disease in the biliary system to which the allergic state is secondary. Experimental evidence (2) points to the fact that antigens localize in inflamed areas, therefore, biliary passages which are primarily infected may become the organs which are attacked by a secondary allergy (3). This secondary allergy may confine itself to the infected biliary system or it may, in addition, become the cause of a subsequent development of bronchial asthma. Indeed the allergic state may become so prominent that it alters the picture of primary organic disease in the gall bladder and ducts.

In treating a patient in whom the diagnosis of bronchial asthma is correct and who may show as well a complex and not entirely definite picture of a right upper quadrant syndrome, thought and care must be exercised before operation is advised (4). If in asthmatic patients on whom a diagnosis of a complicating cholecystitis has been made, a diseased gall bladder is not found, then drainage or cholecystectomy may neither relieve the abdominal symptoms nor the asthma. But if, after careful consideration and long observation, the decision is reached that the gall bladder may be the site of actual disease and that, in addition, it is playing the major role in a spasmophilic state, cholecystectomy may result in a cure of the asthma.

Two patients with bronchial asthma have been followed for a long period of time, and in both cholecystectomy was done. Their histories, though quite different, reveal interesting phases in the relationship of the asthma to the abdominal symptoms.

CASE REPORTS

Case 1. History. A 36 year old married woman was admitted to Montefiore Hospital in March, 1933. She was perfectly well until seven years before admission, when, in the summer of 1926, she experienced a sudden attack of violent sneezing which progressed through a three month period into what was probably hay fever, with tickling in the throat, watery eyes and persistent sneezing. In November she commenced to have difficulty in breathing, her chest felt "heavy," she developed a cough and noticed "whistling" in the chest. About this time her asthmatic seizures began, with sudden and extreme difficulty in breathing, once or twice a day, more often at night. These episodes occurred in the house or outdoors, in good weather or bad, and shortly afterwards she experienced the first attack of sharp, right upper quadrant pain, radiating to the back. She was pregnant, and this was terminated normally in April, 1927. After delivery, the asthmatic attacks became more frequent but were quickly relieved by adrenalin. Between July, 1927, and her admission to Montefiore Hospital in March, 1933, she had had several admissions to other hospitals, where diagnoses of bronchial asthma, ethmoiditis and cholecystitis were made. Operations were performed upon the sphenoid and both ethmoid sinuses, and courses of autogenous vaccine and foreign protein therapy were administered. Innumerable skin tests indicated sensitivity to so many things that it was considered impractical to impose restrictions or to carry out treatment on the basis of these findings. In August, 1932, while at one hospital, she suffered an attack of broncho-pneumonia, and was free of asthma during this period. In

addition to the asthma, she complained of constant fulness in the epigastrium after meals, considerable belching, and frequent attacks of right upper quadrant pain, radiating to the back. She had never been jaundiced or had clay-colored stools. There was no family history of allergic diseases. Her menses were normal and two pregnancies terminated in normal births. She was admitted with complaints pertaining to the asthma, precordial pain, pain in the wrists, loss of seventy pounds in weight over a period of years, and extreme weakness.

Examination. The patient was a poorly developed, markedly undernourished woman, pale and dehydrated. There was emphysema of the chest and tenderness in the right upper quadrant of the abdomen. An admission diagnosis of bronchial asthma and chronic cholecystitis with cholelithiasis was made.

Course. During her stay in the hospital she experienced at least fifteen asthmatic seizures daily. Relief was obtained by large and repeated doses of adrenalin, but at times only morphine would control an attack. Routine laboratory studies were negative. X-ray pictures of the chest showed pleural thickening in both costophrenic sinuses, a diffuse fibrosis at both bases and a hypoplastic type of heart. X-ray studies of the biliary tract were negative. A careful psychological study revealed a number of deep-rooted psychogenic factors. She was discharged in July, 1933, to the Sydenham Hospital for inhalation therapy. Here also, tests showed a multitudinous sensitivity to foods and drugs. As much as 25 cc. of adrenalin was required daily to prevent the condition of *status asthmaticus*. While at the Sydenham Hospital she had several gall bladder attacks. X-ray examination on one occasion did not visualize the gall bladder. Inhalation therapy caused some diminution in the severity and frequency of the asthmatic attacks. She was able to remain at home until January, 1934, when she was again admitted to Montefiore Hospital.

Second Admission. At this time her menses had become irregular but there was no apparent pelvic disorder. There were no signs of circulatory failure present or of a pulmonary infection. After examination of the nose, throat and sinuses no further surgical intervention was advised. Her asthmatic attacks continued. In February, 1934, she presumably had a broncho-pneumonia, during which her asthma lessened in severity and she required no adrenalin. An extensive investigation, carried out under the direction of Dr. Joseph Harkavy, disclosed sensitivity to a great variety of foods and pollens. Attempts at elimination diets proved of no avail. Her asthmatic attacks persisted. She often reverted to a condition of *status asthmaticus*, and she continued to be a most difficult therapeutic problem. At times adrenalin was given to the point of extreme palpitation and twitchings without relief. In September, 1934, a right sphenopalatine block was resorted to, without effect. Every possible therapeutic agent was used but her condition remained essentially the same.

On August 19, 1935, she had an attack of what was presumably acute cholecystitis, with a temperature of 102°F. and with pain and tenderness in the right upper quadrant of the abdomen. This attack subsided in a week. X-ray studies were negative. When, in May, 1936, another similar attack occurred, the surgical service, while recognizing the complexity of her case, believed the gall bladder to be the site of a chronic infection and advised cholecystectomy. She refused operation.

In April, 1937, she had a severe attack of right upper quadrant pain. The liver and gall bladder region were extremely tender, and a mass could be felt. Recognizing the gall bladder as a possible asthmogenic organ, operation was again advised and this time she consented.

Operation. A cholecystectomy was done under basal avertin and local anaesthesia, supplemented with nitrous oxide. Numerous adhesions were found between the gall bladder and the stomach, duodenum and transverse colon. The gall bladder

itself was not thickened and contained no stones. The liver appeared grossly normal. Section of the gall bladder revealed no chronic disease.

Course. Her postoperative course was uneventful, and during the beginning of this convalescent period of about three weeks no asthmatic attacks occurred. Toward the close she had two or three seizures a day, relieved at times by a sterile hypodermic injection or by a small dose of adrenalin. She was discharged from the hospital at the end of her postoperative period.

Follow-up. This patient has been followed up to date. Since the operation her asthmatic attacks have been much less frequent and much less severe. She has not needed hospitalization again. She remained at home, administered adrenalin to herself when necessary, and had the aid of oxygen therapy at times until she finally was able to be up and about, to do housework and to undertake the care of her children. For the past year she has lived in Florida where her husband has obtained employment and where she has set up a household. She reports that the climate agrees with her and that her asthma is under control, though she does not consider herself as cured.

Case 2. History. A 63 year old woman was admitted to Montefiore Hospital on January 17, 1937. She had had attacks of frank bronchial asthma for several years, the attacks becoming much more frequent in the past six months. There were several previous admissions to Montefiore and Sydenham Hospitals, where the diagnosis of bronchial asthma, arteriosclerosis and chronic cholecystitis with cholelithiasis was made. In September, 1935, she entered the Sydenham Hospital with a history of loss of forty-five pounds in weight, mid-epigastric pain, nausea and vomiting. She had frequent asthmatic seizures with wheezing and extreme dyspnea. Tests done prior to admission showed her to be sensitive to a great many foods and pollens, but injection therapy effected no relief. Although there were no definite physical findings it was thought that she might have a malignancy, but all studies of the gastro-intestinal tract were negative. Inhalation therapy gave her temporary relief. Her first gall bladder attack occurred in 1934, with acute pain in the right upper quadrant, radiating to the right shoulder, nausea, vomiting, chills and fever. A number of similar biliary attacks occurred between 1934 and 1937.

Examination. On admission, she presented besides asthma, acute tenderness in the right upper quadrant, with muscular rigidity, and a tender mass could be felt in this region.

Laboratory Data. After subsidence of the acute symptoms, X-ray examination showed a non-functioning gall bladder, containing a large stone. Other laboratory studies were negative.

Operation. A cholecystectomy was performed on January 26, 1937 for chronic cholecystitis with cholelithiasis. The gall bladder was subacutely inflamed, enlarged, markedly thickened and adherent in a mass to the stomach, duodenum and transverse colon.

Course. Her postoperative course was satisfactory and her asthmatic attacks were abruptly controlled. She was discharged apparently well on February 28, 1937. Since that time she has had no further asthmatic seizures. About a year ago she suffered a cerebral hemorrhage from which she recovered, with a residual hemiplegia. She has no abdominal complaints, eats a full diet, and has regained normal weight.

COMMENT

In the first case, operation was resorted to reluctantly, since there was no assurance that cholecystectomy would be of help. Improvement

since operation has been progressive and continuous, but this is not attributed to the surgical procedure, although something did happen to interrupt the constant chain of impulses that initiated the asthmatic seizures. On previous occasions, when she had fever, as during her attacks of broncho-pneumonia, the asthma subsided, but only for a short time. However, treatment with foreign protein and hyperthermia were not successful. The complicated psychological status of this patient is recognized, and it can now be stated that with an improvement in her home surroundings and economic condition, a cause of mental agitation has been removed. Taking into account all the recognized factors that may have influenced her asthma, which became an almost continuous phenomenon, surgical intervention did something to break the chain of events. Whereas operation is believed to have been the determining factor for a considerable improvement of the asthma, it cannot be decided, logically, that it resulted in a cure.

The second patient is a happy woman, with no interfering psychological factors. Her asthma was debilitating and at one time reduced her to chronic invalidism. Chronic cholecystitis with cholelithiasis complicated her disease. In this case a good result was anticipated by operation, and cholecystectomy is believed to have been the decisive factor which resulted in a cure of the asthma. She has been free of all asthmatic symptoms for over three years.

SUMMARY

Two cases of asthma are presented, and the relationship of abdominal symptoms to this disease is discussed. Cholecystectomy was done in both cases. The conclusion is reached that in one case the operation resulted in a cure of the asthma and in the other, operation influenced favorably the future course of the disease.

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RADIOLOGY AND RADIOTHERAPY COMBINED CONFERENCE

MARCY L. SUSSMAN, M.D., *presiding*

January 4, 1940

Case 5.[1] Paget's Disease: Renal Calculi

[*From the Surgical Service of Dr. A. Hyman*]

History (Adm. 451072). A white, married woman, aged 45 years was admitted to the hospital on August 24, 1939. The chief complaint was dysphagia for eight months. Three months before admission she noticed an enlargement of the neck in the region of the thyroid gland. At that time she also became extremely nervous and irritable. She went to a private physician and a basal metabolic rate was reported as plus 40 per cent. Medication given by her physician brought relief of her dysphagia. She was admitted because the dysphagia recurred. Ten years before admission she was told that she had a "floating kidney" on the right side and was advised to wear a belt. Five years before admission she experienced left loin pain and passed cloudy urine. She was told that she had bilateral renal calculi, too large for removal. There were no subsequent renal symptoms. However, there were intermittent periods of painless swelling of the lower abdomen with occasional episodes of tenderness.

Examination. The patient was undernourished and pale with moderate exophthalmos. The temperature was 98°F.; the respirations 22 per minute; the pulse rate 128 per minute and the blood pressure 110 systolic and 70 diastolic. The right lobe of the thyroid was enlarged to the size of a large cherry. There was a fine tremor of the hands. The abdomen was distended on the right side with a large, smooth, non-tender mass in the right flank.

Laboratory Data. The white blood cell count was 7,500 with a normal differential count. The sedimentation time was 7 minutes. The urine contained 1 plus albumin but no sugar; there were many clumped white cells in the sediment. Culture of the urine showed B. proteus. Two basal metabolic rate determinations were plus 16 and plus 12 per cent respectively. Cystoscopic examination of the genito-urinary tract revealed non-function of the right kidney and good function of the left (fig. 12). There were calculi in both kidneys.

Course. A right subcapsular nephrectomy was performed on September 19, 1939. The specimen revealed acute and chronic calculous pyonephrosis. The patient did well postoperatively. Radiographs of the patient's skull were made as the result of a technical error and surprisingly revealed a thickening of the calvarium with alternating rarefaction and opacity (fig. 13). The remainder of the skeleton

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

showed no abnormalities radiographically. The amounts of calcium and phosphorus in the blood were within normal limits on three occasions. The phosphatase was 15, 25 and 22 King-Armstrong units on separate occasions. Calcium balance studies were

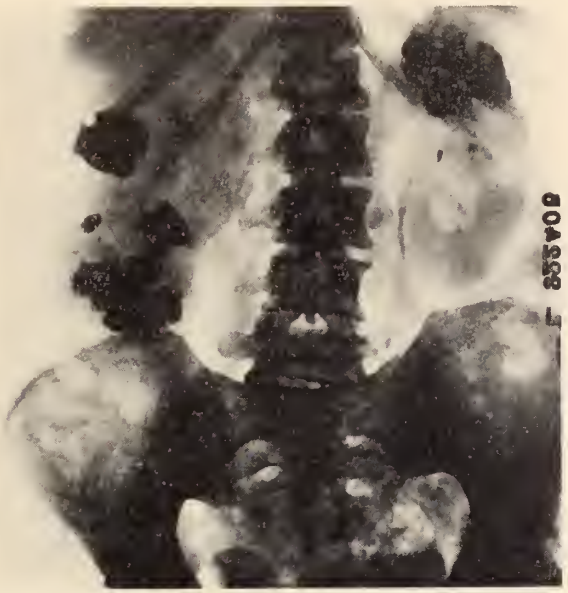

FIG. 12. Case 5. Bilateral renal calculi with bilateral pyonephrosis. There were no definite changes in the spine or pelvis.

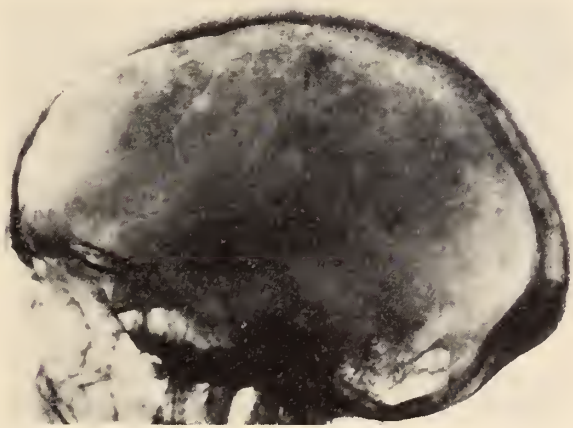

FIG. 13. Case 5. Thickened calvarium with alternating areas of rarefaction and opacity suggesting Paget's disease.

made on September 14 and October 17. The first examination showed an average excretion of 220 mg. per day over a three-day period and the second 137 mg. per day on an intake of 110 mg. of calcium per day. It was deemed advisable, therefore, to enucleate the thyroid adenoma and, at the same time, to explore the neck for para-

thyroid tumor. On November 1, 1939 exploration revealed four normal-sized parathyroids. The discharge diagnosis was Paget's disease with renal calculi.

Tabular Summary of Laboratory Findings

DATE	BLOOD Ca	BLOOD P	PHOSPHATASE K-A	SER. ALB.	SER. GLOB.	TOT. PROT.	BLOOD UREA N
	mg. %	*mg. %*	*units*	*mg. %*	*mg. %*	*mg. %*	*mg. %*
8–25–39							13.0
8–29–39	9.8	3.1	15.0				
9– 4–39	9.3	4.0				6.9	
9–15–39			25.0	4.4	2.6	7.0	
9–20–39							13.0
10–23–39	9.3	4.1	22.0				
1–12–40	10.8	4.6	33.0	4.9	2.2		

Second Admission. The patient was re-admitted on January 12, 1940 for a left nephrolithotomy. During the interval period at home she gained in weight and strength. There were no symptoms referrable to the urinary tract.

Examination. The patient was well developed and well nourished. There was definite exophthalmos. There were well healed right nephrectomy and thyroidectomy scars. The left kidney was definitely enlarged on palpation.

Laboratory Data. The white blood cell count was 7,500 per cubic millimeter. The hemoglobin was 75 per cent. The urine contained 1 plus albumin but no sugar. There were many white blood cells and 5 to 10 red blood cells per high power field in the sediment. The basal metabolic rate was minus 2 per cent.

Course. A left nephrolithotomy was performed on January 23, 1940. The patient developed abdominal distention on the second postoperative day. On the fourth day there was no urine in the bladder. She ran a septic fever throughout her entire postoperative course. On the eighth postoperative day a blood culture showed hemolytic streptococcus; the blood urea nitrogen rose to 45 mg. per 100 cc. On the ninth day the patient suddenly went into shock, and in spite of supportive measures, quickly died.

Necropsy Findings. The findings of significance which were noted were:

1. A congenital malformation of the left *kidney* with excessive rotation and posteriorly situated pelvis.
2. An acute and chronic pyonephrosis and pyelonephritis of the left kidney.
3. Two normal parathyroid glands on the non-operated side; no parathyroid glands identified on the operated side.
4. A patchy bronchopneumonia.
5. Essentially normal *bone* from vertebrae and ribs. The skull was not examined.

Comment. Dr. M. L. Sussman: Roentgenograms of the skull showed thickening of the bones of the calvarium, particularly the parietal bones. There was irregular decalcification of this bone in association with irregular areas of ossification. The remainder of the skeleton which was examined showed no abnormalities. In spite of the presence of bilateral renal calculi the roentgen findings along with the normal figures for calcium and phosphorous content in the blood suggested Paget's disease in the skull. This was confirmed by subsequent surgical exploration of the neck and by autopsy. It is interesting to note that there was a mild negative

calcium balance on two repeated occasions. The significance of this is difficult to evaluate. A patient subjected to bed rest over a long period of time may present a negative calcium balance. In addition, there was a functioning left calculus pyonephrosis which may have contributed to the excess calcium in the urine.

Case 6. Renal Osteitis Fibrosa

[*From the Pediatric Service of Dr. B. Sehick*]

History (Adm. 405664). A white female child, aged 12 years, was admitted to the hospital on March 11, 1937 with a history of increasing dyspnea, weakness and difficulty in walking for ten months. The child always suffered from a moderate degree of polyuria and polydipsia since an attack of pyelitis in infancy. She had always been obese. At 19 months of age a private physician told the mother that the child's spleen was enlarged and a possible correlation was suggested with the fact that the father had died of Hodgkins' disease. Ten months before admission the mother noticed that the child was becoming "knock-kneed" and the child complained of pains in the knees and ankles. At this time the child was taken to the Out-Patient Department where roentgenograms of both hips were made but failed to reveal an abnormality. She was treated in another hospital with no improvement. Then she was kept at home and went downhill steadily with increasing weakness and pallor. One week prior to admission the child complained of a severe, sharp, sticking pain in the left upper quadrant.

Examination. The child was short in stature with a markedly obese trunk and slender extremities. The temperature was 98.6°F, the pulse rate 110 per minute, respirations 24 per minute. There was a lemon-yellow tint to the skin somewhat obscured by the effects of previous Alpine Light Therapy. There were several pigmented hairy naevi on the face. There was marked genu valgum. The child was unable to walk without help. The fundi showed slight narrowing of the arteries. The heart was slightly enlarged to the left. There was a soft apical systolic murmur. The blood pressure was 120 systolic and 80 diastolic. The abdomen was markedly obese. There was tenderness and muscle spasm of the left upper quadrant. A large mass was palpable in the left kidney region. The liver was palpable two finger-breadths below the costal margin.

Laboratory Data. The blood calcium was 11.7; the blood phosphorus 6.7; the blood urea nitrogen 125.0 mg. per cent, the total protein 7.7 gm. per cent; the creatinine 5.0; the chlorides 470 and the sugar 105 mg. per cent. The blood sugar tolerance curve was elevated and prolonged. The urine showed albumin three plus and an occasional white cell in the sediment; there was no evidence of glucose. There was a fixation of the specific gravity at 1.008 to 1.010. The phenolsulfonphthalein test was less than 5 per cent excretion in 2 hours. The hemoglobin was 32 per cent, the red blood count was 2.5 million per cubic millimeter. The blood smear showed a severe hypochromic anemia. Skin tuberculin and blood Wassermann reactions were negative. The visual fields were negative. An electrocardiogram showed an enlarged P-I with inversion of T-3 and high voltage in all leads. Roentgenograms

of the hips, knees and elbows revealed the presence of a marked erosion in the region of the metaphyses with deformity. The bones of the skull showed evidence of generalized osteoporosis. A diagnosis of renal rickets was made.

Course. The patient did poorly during her stay in the hospital. Her temperature ranged between 99 to 101°F. during most of this period. One month after admission calcific deposits appeared in the subcutaneous tissues: first in the sacral region, then over both lower extremities. During this time the blood calcium was lower than on previous occasions. Shortly afterward, marked beading of the ribs appeared. About six weeks after admission, large subcutaneous calcified masses appeared in the sternoclavicular regions. She was transfused three times with no response. A low protein diet had no effect on the general condition of the patient. On a high caloric, low phosphorus diet for three weeks the blood urea nitrogen was lower but the calcium and phosphorus remained the same. The patient was discharged June 29, 1937 in poor condition.

Second Admission. The patient was re-admitted on July 6, 1937. During the nine days at home she had done poorly. She had been quite listless and complained of abdominal pain. Cyanosis of the extremities became very marked. The child voided practically no urine and when admitted was practically moribund.

Examination. There was a loud systolic murmur over the entire precordium. The lung fields were clear. No blood pressure or radial pulse could be obtained.

Laboratory Data. The red blood cell count was 1,500,000 per cu. mm.; the hemoglobin was 32 per cent; the white blood cell count was 22,700 per cu. mm. with 89 per cent polymorphonuclear leucocytes and 11 per cent lymphocytes. The urine contained 3 plus albumin with many granular casts in the sediment. The blood urea nitrogen was 178 mg. per cent; creatinine 16 mg. per cent; uric acid 12 mg. per cent; calcium was less than 2 mg. per cent and the phosphorus 8 mg. per cent.

Course. In spite of intensive supportive therapy the child failed to respond and died about 18 hours after admission. An autopsy was not performed. The clinical diagnosis was renal osteitis fibrosa with polycystic kidneys.

Tabular Summary of Laboratory Findings

DATE	Ca	P	PHOSPHAT. K-A	SER. ALB.	SER. GLOB.	UREA N	CREAT.	TOT. PROT.	
	mg. %	*mg. %*	*units*	*mg. %*	*mg. %*	*mg. %*	*mg. %*	*mg. %*	
3-12-37	11.1	6.7		5.2	2.5	125.0	5.0	7.7	1st admission
3-17-37			12.0						
3-23-37	11.3	5.2	11.0			145.0			
4-13-37	9.8	4.0		4.6	2.9	110.0	5.0	7.5	Appearance of subcutaneous calcifications
4-24-37	12.5								
5- 4-37	12.1	8.5	13.5	3.0	3.1	91.0		6.1	
5-22-37	10.6	7.5		4.2	1.9	80.0		6.1	
6- 1-37	11.7	6.6				49.0			Low protein diet
6- 7-37						70.0			
6-13-37	10.1	8.0				88.0			
6-21-37	10.5	9.2				120.0		7.0	
6-23-37						105.0			
6-25-37						135.0			
6-27-37	11.1	8.0		4.6	2.3	100.0		6.9	Discharged to home
7- 7-37	12.0	8.0	12.0	5.3	1.8	178.0	16.0	7.1	Day of death

Comment. Dr. M. L. Sussman: The long bones in this case show the typical changes of "renal rickets"; namely metaphyseal deformity and compression with irregular decalcification (fig. 14). The vertebral bodies show the same tendency to decalcification in the central portion with increased density of the juxtarticular portions that are seen in primary hyperparathyroidism (fig. 15). Evidence of generalized decalcification is not prominent. The skull does not show the miliary changes character-

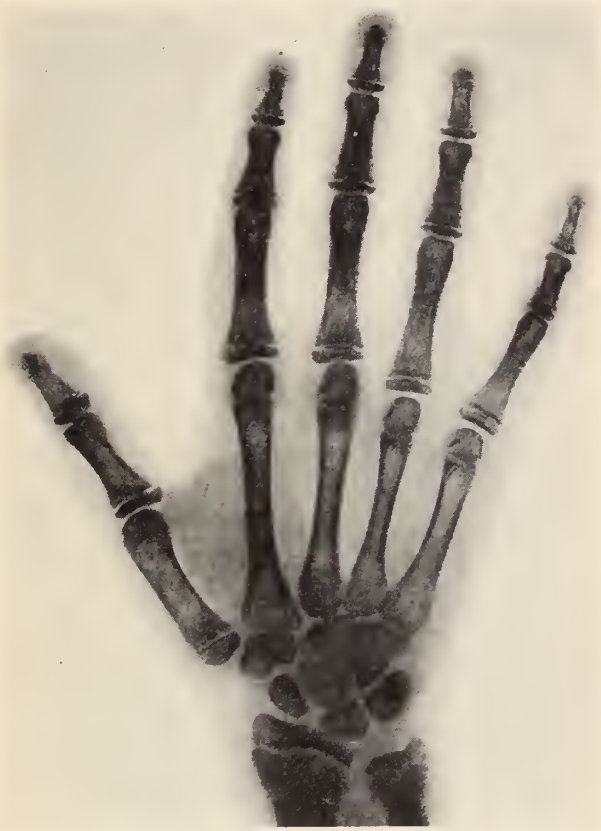

Fig. 14. Case 6. Deformity of the ends of the long bones due to decalcification and irregularity of the metaphyses.

istic of primary hyperparathyroidism. An interesting finding was the demonstration of rapid calcification of the vessels as well as masses of what presumably are calcification at the junction of bony and cartilaginous portions of the ribs (fig. 16).

The phosphorous content of the blood was elevated above normal which is characteristic of the renal insufficiency.

Reported by *Harold G. Jacobson, M.D.*

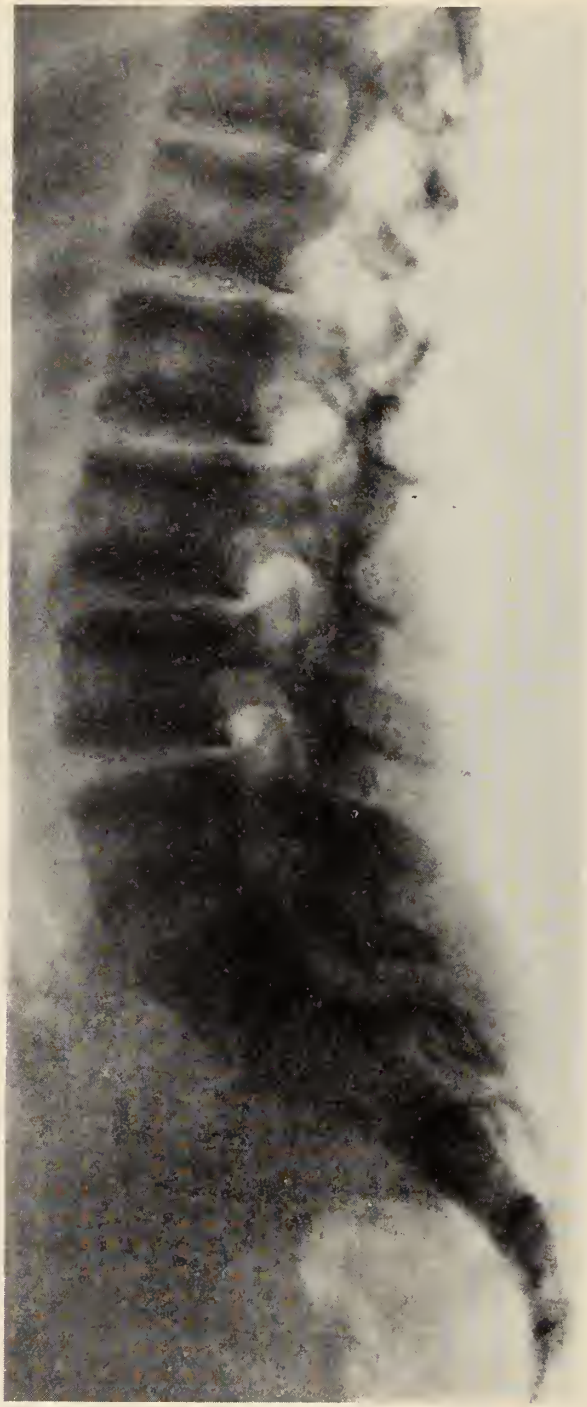

FIG. 15. Case 6. Decalcification of the centers of the vertebral bodies with relative increased density of the subarticular portions.

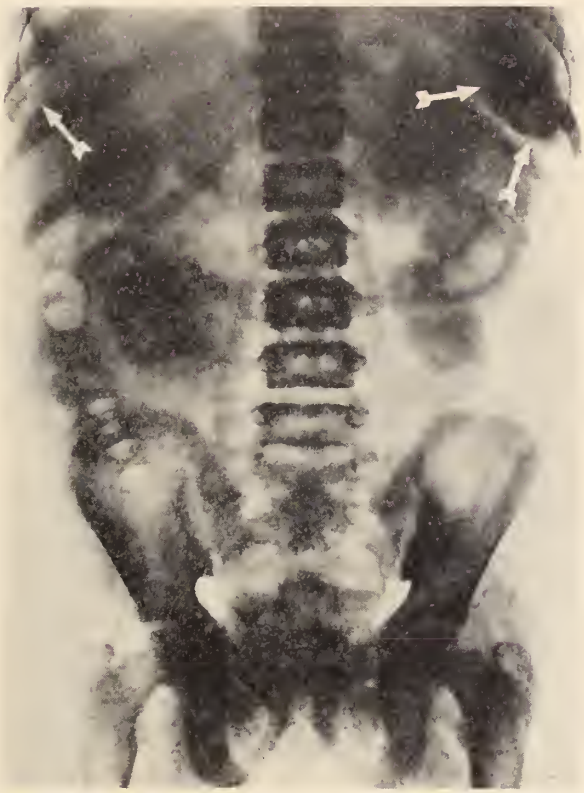

FIG. 16. Case 6. There is marked bilateral coxa vara deformity with decalcification of the metaphyses of the long bones. Club-like calcifications of the costochondral junctions are noted (arrow). Marked calcification of the blood vessels and subcutaneous tissues.

CLINICAL PATHOLOGICAL CONFERENCE

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

Wednesday, October 25, 1939

Fulminating Meningococcemia without Meningitis; Death within Fourteen Hours after Onset; Adrenal Hemorrhages

[*From the Pediatric Service of Dr. Bela Schick*]

History (Adm. 445488; P.M. 11253). This was the first admission of a 3 year old male child. His birth and development were normal. His family and past histories were irrelevant. The child was well until eight hours before admission. At that time he complained of some pain in the right thigh. The mother noticed a limp. She carried the child upstairs and noted that he was shivering, and felt cold. His temperature was found to be 103°F. The respirations became rapid and the lips cyanotic. He was given an enema, but the temperature continued to rise. He vomited five or six times and was then brought to the hospital.

Examination. The child was well developed and well nourished. He appeared somnolent and hyperacutely ill. The temperature on admission was 107°F. Respirations were rapid and grunting; there was slight ashy cyanosis. Slight tenderness and spasm were present in the right upper quadrant with no rebound. The heart sounds were distant and very rapid. The pulses were not palpable. A few medium moist râles were heard scattered throughout the lung fields. There was a scattered macular eruption over the trunk which was confluent on the right side of the neck. The deep reflexes were depressed; the abdominal reflexes were absent; the cremasteric reflexes were sluggish; the Kernig and the Brudzinski signs were equivocal. There was marked injection of the conjunctivae and slight injection of the left ear drum. The tongue was coated; the pharynx was injected.

Laboratory Data. The hemoglobin was 80 per cent. Red blood cell count, 5,200,000; white blood cell count, 5,000 (31 per cent polymorphonuclear neutrophiles; 66 per cent lymphocytes and 3 per cent monocytes). Urine was not obtained.

Course. It was felt that the child had an overwhelming sepsis. To clarify the diagnosis, an X-ray examination of the chest was done on the way to the ward. This was reported as negative. On arrival at the ward, a lumbar puncture was done. This revealed crystal clear, colorless cerebrospinal fluid at a pressure of 240 mm. of water. The Pandy test was negative. There were 6 red cells (traumatic ?) and 4 white cells per cubic millimeter. Cerebrospinal fluid chemistry showed sugar, 55; chlorides, 770; and protein, 25. A blood culture was immediately taken. This was later reported to be positive for meningococci.

His condition rapidly became worse, with increasing cyanosis and increasing weakness of heart action. Suction was necessary to clear the respiratory passages of rapidly accumulating thick mucus. While under observation the erythematous

lesions noted on admission took on a purpuric character. In some areas they became confluent, resembling post mortem lividity. In spite of intravenous fluids, stimulants, and a 300 cc. blood transfusion, the child rapidly became worse and died. Death occurred six hours after admission, and fourteen hours after the onset of the illness.

Necropsy Findings. Dr. Klemperer: The internal organs showed relatively little. There was no meningitis. A few petechial lesions were present on the various serosal surfaces. The *adrenals* were enlarged and diffusely hemorrhagic, giving a typical picture of hemorrhagic infarction of the adrenal. This picture is common in meningococcus sepsis occurring in children. Histologic examination of the skin petechiae showed cocci in the capillaries and adjacent tissue. Aspiration of the petechiae could demonstrate the bacteria for diagnostic purposes. Similar lesions could be seen in other petechial areas throughout the body, as in the stomach mucosa and myocardium.

Comment. Dr. Baehr: As was originally reported by Dr. W. W. Herrick of this city, meningococcemia usually precedes a meningococcus meningitis. Recovery from the bacteremia itself is common, the meningitis remaining as a metastatic lesion. In infants meningococcemia may be overwhelming and meningitis need not occur. To make the diagnosis there is usually no need to await the blood culture. Scrapings from a purpuric spot will usually demonstrate the gram-negative cocci. In older patients, meningococcemia may persist for months and end in recovery. It is usually, but not necessarily, secondary to an endocarditis. Some years ago I had a young patient with persistent meningococcemia which lasted for ten weeks. Finally, in desperation, an attempt was made to desensitize her by injecting minute amounts of diluted serum. On the very first injection of one drop of serum intravenously, the patient went into profound anaphylactic shock, the pulse and blood pressure became imperceptible, and the temperature mounted to 107°F. It then dropped precipitately to normal, thereafter remained absolutely normal, and the child walked out of the hospital ten days later. The cure was effected with one drop of serum. Such phenomenal cures are not rare in meningococcemia either after the use of non-specific therapy or spontaneously. There is reason to believe that the therapeutic effect of serum therapy in meningococcus meningitis may be largely non-specific.

Dr. Schick: This picture of purpura in blood infections and associated adrenal hemorrhages is common in infants. It is called the Friederick-Waterhouse syndrome. Seventy per cent of the cases occur in children below two years of age. Sixty per cent are caused by the meningococcus and the rest are due to the pneumococcus, and the streptococcus; a few have negative blood cultures. During severe scarlet fever and diphtheria, adrenal apoplexy may also occur. This most likely is due to the effects of the toxin. In animal experiments similar lesions have been produced with diphtheria toxin. In this country such cases are extremely rare because of the relative mildness of these diseases.

Cushing's Syndrome Due to Adenoma of Adrenal Cortex; Death after Adrenalectomy Caused by Secondary Atrophy and Adrenal Insufficiency of the Opposite Adrenal; Pituitary Basophilism Secondary to Hyperfunction of the Adrenal Adenoma

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

History (Adm. 435550; P.M. 11111). The patient, a 30 year old woman, was admitted to this hospital on January 30, 1939 with a chief complaint of weakness in both legs of three months' duration. Seven months prior to admission amenorrhea was noted. A diagnostic curettage was done with no significant findings. Four months before admission she noted severe bilateral lower back pain. One month later the right leg became numb from the ankle to the knee. This abated after a few weeks, but the patient then noted weakness in the left knee which became progressively more severe. Ultimately the right lower extremity became involved. Her sensory perception remained intact. Approximately two weeks before admission she had mild flexor spasms about the left knee. In the months preceding admission there was urinary urgency but the patient did not notice any polyuria. She had also noted during the course of her illness, the appearance of small purple striae in the abdominal wall and a tendency toward purpuric hemorrhages in the skin. There had been a moderate weight loss in spite of the fact that she noted increased fat deposits in the face and trunk. The extremities appeared thinner.

Examination. The patient was well developed and well nourished. The abdomen, neck and face were obese; the extremities were thin. The skull was of normal contour and there was no percussion tenderness or other abnormality. The blood pressure in all extremities was 170 systolic and 120 diastolic. No masses were demonstrable in the abdomen. A small umbilical hernia was present. The skin was flushed and there were many prominent venules over the legs and chest with numerous ecchymoses over the legs. There was slight pitting edema of the legs and moderate hirsutes of the face and neck. A complete neurological examination revealed a waddling gait and diminished to absent deep reflexes in the lower extremities. The lower abdominal reflexes were not obtained. There was slight atrophy of the upper thigh muscles. The clitoris was large.

Laboratory Data. The hemoglobin, 99 per cent (Sahli); red blood cell count, 5,200,000; white blood cell count, 7,900 (normal differential). The blood chemistry findings were as follows: albumin, 4.8 and globulin, 1.6 Gm. per 100 cc.; phosphorus, 3.7 mg. per 100 cc.; calcium, 10.6 mg. per 100 cc.; phosphatase, 13.7 King-Armstrong units. A lumbar puncture was performed and was negative except for a 4 plus Pandy. A glucose tolerance test revealed a diminished tolerance. Examination of the urine was negative. The blood Wassermann and Kahn reactions were negative. A sternal aspiration was performed and found to be normal. An intravenous pyelogram showed a normal right urinary tract. The left tract was not well visualized. X-ray examination of the skull revealed mottled, irregular destruction of the frontal bone with similar though less marked changes in the rest of the skull. The sella turcica was normal. X-ray examination of the rest of the bones showed marked decalcification. Right perirenal insufflation showed a normal adrenal. This pro-

cedure, when repeated on the left, showed an enlarged adrenal suggestive of an adenoma. An electrocardiogram revealed left ventricular preponderance and mild myocardial disease. X-ray examination of the chest was not significant. A muscle biopsy from the thigh showed the tissue to be infiltrated with lymphocytes.

Course. The laboratory and clinical investigations all pointed towards a Cushing's syndrome secondary to an adenoma of the left adrenal cortex. The patient was operated upon and a golf-ball sized tumor removed. Postoperatively she was treated with high salt intake and cortin. Shortly after operation the temperature rose and some râles at the bases of both lungs developed. X-ray examination of the chest revealed slightly increased markings at both bases. Subsequent examinations of the chest suggested the presence of fluid in both pleural spaces. Thirty cubic centimeters of fluid were aspirated and found to be negative on smear and culture.

FIG. 1. Contralateral atrophic adrenal (lower figure), compared with a normal adrenal (upper figure)

The patient ran a high temperature and the wound was laid open to see if there was deep infection. The blood chlorides as sodium chloride was 585 mg. per cent at this time, and the calcium dropped to 8.3 mg. per cent. The fluctuating temperature, dyspnea and cyanosis continued and the patient's course went progressively downhill. She died three weeks after operation.

Necropsy Findings. Dr. Klemperer: Examination of the left *adrenal* removed at operation showed it to be a tumor the size of a golf ball. Histologically it was an adrenal adenoma. The right adrenal weighed only 7.5 grams, and on microscopic examination showed marked narrowing of the zona glomerulosa and some atrophy of the zona reticularis and zona fasciculata. The *pituitary* gland was not enlarged, but, on microscopic examination, distinct hyaline changes as described by Crooke were seen in the basophilic cells. The *lungs* showed a pneumonic process in both lower lobes. The *bones* were the seat of a striking degree of osteoporosis with atrophy of the bony trabeculae. The *ovaries* were small, atrophic, with absence of any corpus luteum.

Comment. Dr. Wechsler: The initial complaints of this patient were due to a radicular syndrome secondary to partial collapse of the vertebrae and compression of the nerve roots. This in turn was secondary to the marked osteoporosis. In Cushing's syndrome, whether it is a result of

adrenal or pituitary pathology, the clinical picture would seem to be a composite of the simultaneous influence of both glands. Thus, the hypertension and glycosuria may well be traced to the adrenal, and obesity and decalcification are probably manifestations of pituitary influence.

Dr. Klemperer: The distinct hyaline changes in the basophilic cells of the pituitary do not necessarily point to this as the cause of the syndrome. Rather, they merely indicate that certain changes take place in the pituitary gland in association with tumors of other endocrine glands. The unusually small size of the contralateral adrenal gland is extremely important. In another case of this kind, the uninvolved adrenal gland weighed only 5 grams. This finding may account for the development of postoperative symptoms of adrenal insufficiency that have been observed in these cases.

Dr. Baehr: The demonstration of marked atrophy of the cortex of the uninvolved adrenal is significant both from the clinical and therapeutic viewpoint. It appears that when there is active hyper-secretion from an adrenal tumor, there is a reverse effect in the other adrenal cortex. The cortex of the opposite adrenal becomes atrophic. The practical application of this observation lies in the fact that postoperatively, all these cases should have supportive adrenal therapy in the form of a large salt intake and administration of corticosterone.

Today, there is no longer any reason for thinking that all cases of Cushing's syndrome are secondary to basophile adenomas of the pituitary. In this instance as in so many others, the adrenal neoplasm is the primary responsible factor, and the pituitary basophilism is secondary. There is a reciprocal relationship between the pituitary and the adrenal. Cases of hyper-functioning adrenal adenoma or carcinoma will usually show secondary basophilic changes in the pituitary. The reverse occurs in hypofunction of the adrenal. Thus, in Addison's disease there is a conspicuous diminution in the basophile cells of the pituitary.

Addison's Disease Due to Tuberculosis of Adrenals; Death from Pneumonia and Congestive Heart Failure

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

History (Adm. 440686; P.M. 11177). *First admission* (October 11, 1938). The patient was a 38 year old American born newspaper man. Fifteen years previously he had worked in close contact with an open case of tuberculosis. Two years later he developed pleurisy following a severe cold. At the Mayo Clinic he underwent an extensive thoracoplasty for tuberculous empyema. At the time of discharge, the wound was still draining. Two years later (11 years ago) he developed painless jaundice for which he was hospitalized for one year. The jaundice eventually cleared and the empyema cavity closed at that time. There has been no recurrence of pleurisy, empyema or jaundice. He was well until three

years ago when he developed bronzing of the skin and marked asthenia. The weakness became so extreme that he finally collapsed. A diagnosis of Addison's disease was made. At this time, he developed a left mastoid infection for which a mastoidectomy was performed. He was then, and has since been, treated with salt and adrenal cortical extract. On this regime he did fairly well. Shortly before admission he developed an acute upper respiratory tract infection associated with pain in the left ear. He was, therefore, hospitalized in the Private Pavilion of this hospital.

Examination. The left ear revealed a full drum with blebs on the surface. There was some swelling over the zygoma and the post-auricular area. The blood pressure was 98 systolic and 60 diastolic.

Laboratory Data. The hemoglobin was 79 per cent; red blood cell count, 4,400,000; white blood cell count, 5,300, with a normal differential count. The urine analysis did not show any abnormal findings. The blood sodium, following 12 hours of intravenous sodium chloride was 129.7 milli-equivalents per liter. X-ray examination of the mastoids showed the left mastoid process to be diffusely clouded, particularly in the zygomatic area.

Course. A myringotomy was performed and pus was obtained. The swelling over the zygoma persisted and the middle-ear discharge became profuse. It was, therefore, deemed advisable to revise the original mastoidectomy. Meanwhile, to cope with the Addison's disease, the patient received 4 cc. of adrenal cortical extract and sodium chloride, bicarbonate, and citrate. In addition sodium chloride was administered intravenously. Under this regime the patient's blood pressure rose from 98 systolic and 60 diastolic to 120 systolic and 80 diastolic; the blood sodium increased to 132.4 milli-equivalents per liter. A complete mastoidectomy was performed. The patient made an uneventful recovery and was discharged on November 3, 1938.

Second Admission (May 19, 1939). In the six month interval he had received cortical extract and salt. He recovered sufficiently to enable him to return to his work three months previously. He continued to work until two days before admission when he developed a head cold. Because of this he stayed in bed, but felt no weaker than usual. On the day of admission his temperature rose to 105°F. and he became extremely drowsy and lethargic. He had never had any similar episodes. He received his usual dose of cortin and salt.

Examination. The patient was acutely ill, tachypneic with flaring of alae nasi, drowsy, and coughing intermittently. The left mastoidectomy scar was well healed; there were no evidences of middle ear infection. Both buccal mucosae showed brownish pigmentation. Trachea was deviated to the right. There was a right thoracoplasty scar present. At the extreme base of the left lower lobe there was relative dulness, slight suppression of the breath sounds and occasional fine crackling râles. The heart was not abnormal. The blood pressure was 90 systolic and 60 diastolic. The breasts were enlarged to about 6 cm. in diameter; the areolae were prominent and dark. The penis was pigmented. The skin was diffusely bronzed.

The clinical impression was Addison's Disease and lobar pneumonia of the left lower lobe.

Laboratory Data. The hemoglobin was 90 per cent; white blood cell count, 11,700 with 61 per cent polymorphonuclear leucocytes, 31 per cent of which were non-segmented. The blood chemistry showed a urea nitrogen of 10 mg. per cent; sugar, 80 mg. per cent; chlorides, 575 mg. per cent; carbon dioxide, 49.9; icterus index, 7. Sedimentation time was 1 hour. The blood Wassermann reaction was negative.

Blood culture yielded no growth. An X-ray examination of the chest, taken in the prone position immediately on admission, did not show any definite abnormality.

Course. In view of the history and physical findings, the patient was treated as a pneumonia, even though X-ray examination failed to reveal a consolidation. Sulfapyridine was administered, 1 gram every three hours. In view of the normal blood chemistry, Addison's disease was apparently not a predominating factor. He, nevertheless, was treated with large doses of adrenal cortical extract parenterally, saline intravenously, and sodium salts by mouth. The temperature dropped sharply from 106° to 102°F., but the clinical picture became worse. The blood pressure dropped to 74 systolic and 52 diastolic. There was a tachycardia of 120 and a respiratory rate of 40. He remained drowsy, became resistive, and began to refuse medication. On the second day of hospitalization, there was noted marked distention of the neck veins, increasing dyspnea, pulsus paradoxus, and a further drop of blood pressure to 62 systolic and 38 diastolic. Venous pressure was 9 cm. Because of the possibility that the picture might be due to cardiac tamponade, a pericardial aspira-

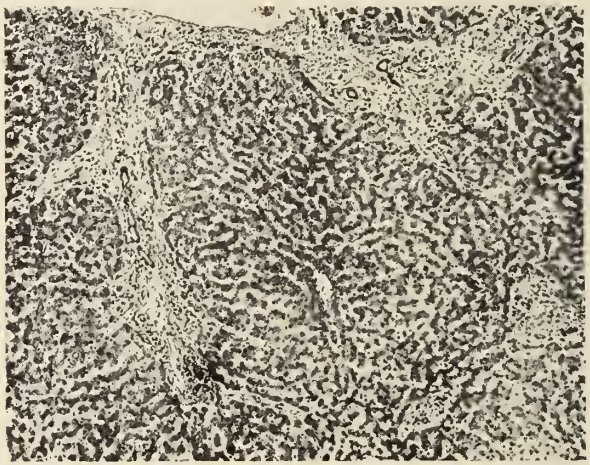

FIG. 2. Liver. Diffuse widening and fibrosis of the periportal spaces with the bile duct increase

tion was attempted. On anterior aspiration of pericardium, only 1 cc. of serofibrinous fluid was obtained. Posteriorly, 40 cc. of fluid was aspirated, which evidently came from the pleural cavity. Smear of this fluid revealed numerous polymorphonuclear leucocytes, but no organisms; culture was sterile. The next day, examination again showed marked distention of the neck veins. The liver was enlarged to the umbilicus and tender. The heart sounds were faint, but the heart did not appear to be enlarged. The picture was interpreted to be due to congestive heart failure, and, therefore, digitalization was begun. However, the patient died within a few hours, after two and a half days of hospitalization.

Necropsy Findings. Dr. Klemperer: Both *adrenals* show typical extensive caseation. The caseation is in the center and is surrounded by extensive fibrosis. This fibrosis is very commonly seen in tuberculosis of the adrenal glands. The *right lung* is collapsed by the previous thoracoplasty and the lung is densely adherent. The left lower lobe is completely involved in a lobar pneumonia. Inasmuch as one lung was compressed, the addition of a lobar pneumonia to the other side caused embarrassment in the lesser circulation. The right side of the *heart* was dilated. Evidence

of acute failure of the right chamber was present. Histologically the heart muscle showed degenerative changes. No primary focus of tuberculosis was demonstrable in the lungs or lymph nodes. The primary infect must have been subcortical with perforation into the pleura thus causing a tuberculous empyema. The *spleen* and *lymph nodes* were enlarged as evidence of a septic state. Grossly the *liver* showed no evidence of the previous episode of jaundice. Histologically, however, there was fibrosis of the periportal spaces with apparent bile duct increase. This is a picture which is very suggestive of an antecedent cholangitis and probably explains the jaundice eleven years ago.

Comment. Dr. Soffer: This patient presented the characteristic findings of Addison's disease. Asthenia, pigmentation, hypotension, low sodium, low chloride, and high potassium were all present. He also showed the typical effect of infection in Addison's disease. These patients have difficulty in handling infection and after recovery their Addisonian state is more severe and they usually need more salt and adrenal extract. With each infection there must be added destruction of adrenal cortex. Before modern therapy such patients could not stand surgery. This patient received 25,000 cc. of saline intravenously and much potent extract before mastoidectomy. The new drug desoxycorticosterol acetate is very effective. This patient did not die of Addison's disease but of lobar pneumonia and right heart failure.

Dr. Baehr: It has been our experience that patients with Addison's disease have weak right hearts. As Dr. Soffer has found, subcutaneous implantation of desoxycorticosterol acetate in patients with Addison's. disease may cause hypertension and precipitate right heart failure. Dr. Robert Loeb of the Presbyterian Hospital has had similar experiences. I must warn you of the indiscriminate use of this drug. It may even precipitate right heart failure, if employed for the treatment of constitutional hypotension in patients with asthenic constitution and drop heart.

Reported by *Max Ellenberg, M.D.*

CLINICAL NEUROPATHOLOGICAL CONFERENCE

JOSEPH H. GLOBUS, M.D., *presiding*

Monday, March 25, 1940

Case 1. Brain Abscess, Due to Infected Paradoxical Embolism

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

History (Adm. 438243; P.M. 11163). The patient was an 11½ year old girl, born a "blue-baby," and known to have congenital heart disease. She had had measles, chicken-pox, and pertussis. She entered the hospital on March 31, 1939, with the history of "bronchitis" three months earlier which was characterized by an unproductive cough and fever of three weeks duration, and that subsequently she received digitalis for a period of three weeks.

Five days before admission to the hospital, the patient developed a right supraorbital headache. Two days later she passed through a clonic seizure affecting the entire left leg. It lasted less than a minute and was not preceded by any aura. Consciousness was retained and there was no loss of sphincteric control. Two similar seizures occurred within three days. Weakness of the left leg was then noted and this was followed by weakness of the left arm, drowsiness, and rise in temperature.

Examination. The patient was very thin, rather tall, and somewhat cyanotic. She rested in bed with the left lower extremity rotated externally and the left arm flexed at the elbow. She was well oriented and cooperative. There was a left hemiparesis, more marked in the arm and minimal in the face and tongue, associated with hyperreflexia and a positive Babinski sign on the same side. All the abdominal reflexes were absent. Muscle-tendon sense was impaired in the left arm and leg. There was a systolic thrill and a harsh systolic murmur over the left third interspace at the sternal margin transmitted over the entire precordium. A2 was louder than P2. Dermatographia was marked over the entire body. Blood pressure was 100 systolic and 60 diastolic. Temperature, 101°F.; pulse, 108 per minute; respirations, 26 per minute.

Laboratory Data. Cerebrospinal fluid: Clear, colorless; initial pressure, 120 mm. of water; Ayala index, 9.6; Pandy test, 4 plus; cells, four red blood cells and three lymphocytes per cubic millimeter; smear of culture, negative. Blood: red blood cells, 6.1 million per cubic millimeter; hemoglobin, 110 per cent; white blood cells, 15,000 per cubic millimeter with predominance of neutrophiles. The Wassermann reaction in the blood and cerebrospinal fluid was negative. X-ray examination of the chest showed the aortic arch to be widened and the heart to be moderately enlarged to the right. X-ray examination of the skull showed the entire occipital and posterior parietal bones to be flat. The blood vessel channels on the right were more prom-

inent than on the left and the Pacchionian granulations seemed to be exaggerated on the right. A calcified pineal was seen approximately in its normal position with a suggestion of a slight displaeement to the left. An eleetrocardiogram was reported as being of the type frequently seen in congenital heart disease.

Course. Four days after admission, the patient eomplained of vertigo and nausea on turning her head to the left, and became inereasingly drowsy. Her headache persisted, although at first she obtained some relief from pressure on the right carotid. The hemiplegia remained unchanged except for the left central faeial paresis which became more marked. On the seventh day photophobia developed; and limitation of left lateral gaze and some nystagmoid jerking on right lateral gaze were noted. Bradycardia as well as hyperemia of the right disc became apparent on the seventh day and the patient slowly sank into a stupor. The clinical diagnosis rested between brain abscess and vaseular aeeident, secondary to an embolic accident, in association with congenital heart disease. The location was thought to be in the right paricto-frontal area, probably subcortical. Encephalography was performed on April 8, 1939. No air was seen in the ventricular system, but some air was noted over the frontal area and in the basilar cisternae. The following day a trephine exploration was performed over the right frontal region and about 70 cc. of thick creamy reddish material was removed. Following the operation, the patient appeared to be much brighter and more alert. A culture of the pus showed small gram-positive cocci in pairs and administration of sulfapyridine was begun. On the thirteenth day in the hospital, the patient began to complain of headache again and vomited several times. Definite blurring of the right disc was noted. She became inereasingly drowsy and on the eighteenth day she suddenly uttered a high-pitched cry and passed into stupor. She responded to an injection of eaffeine sodium benzoate. A lumbar puncture was performed and elear fluid under an initial pressure of 80 mm. of water was obtained. Thirty cubic centimeters of pus was then removed through the trephine opening and air was injected through the opening. X-ray examinations showed the air to be eollected below the trephine defect near the midline in a cavity approximately "1 x 1½" cm. in size. This was presumed to be an extraventricular cavity. The patient continued to be drowsy. Pus was repeatedly aspirated through the original trephine opening. On the nineteenth day the trephine opening was enlarged and the abscess cavity was entered, evacuated, and a rubber drain was inserted. On the twentieth day the patient was more alert, but her temperature began to "spike." The paresis of the left leg became more marked and the patient complained of a generalized head and neck pain. This was accompanied by marked nuchal rigidity. A lumbar puncture on the twenty-fifth day in the hospital yielded xanthochromic, cloudy spinal fluid but did not relieve the headache. On the twenty-eighth day the patient was operated on for the third time and a great quantity of thick yellow pus was evacuated from the right frontal lobe. The patient was returned to the ward in poor condition. A right external reetus palsy developed; on the following day the temperature rose to 106°F. Lumbar puncture on the thirtieth day revealed fluid under pressure of 420 mm. of water. Herniation and a putrid fungus cerebri set in and the patient died on her fortieth day in the hospital.

Necropsy Findings. Brain. Gross. A large herniating mass of brain tissue, the size of an orange was found protruding from an operative defect in the right parietal area. The surface of the herniation was neerotic and hemorrhagie and covered by purulent exudate. On opening the dura, large amounts of liquid yellowish-brown pus poured from the incision. The entire right hemisphere was softened and the frontal pole was replaced by necrotic, purulent exudate. The exudate extended through the subarachnoid space and surrounded the base of the brain and lobes of the cerebellum.

On sectioning the brain, an abscess cavity was found in the anterior portion of the frontal lobe. It was triangular in shape with its longest diameter extending 2½ cm. posterior from the frontal pole (fig. 1). The abscess was surrounded posteriorly, dorso-laterally, and medially by necrotic brain tissue with no apparent attempt at encapsulation. A defect in the mesial wall of the abscess communicated with the ventricular system. The only superficial opening into the abscess was a defect in its anterior extremity communicating with the subdural space and associated with a large collection of pus in that region which compressed the right cerebral hemisphere. The pus obtained by the frequent aspirations probably came from this collection in the subdural space.

Microscopic. Sections of the wall of the abscess and the surrounding brain tissue have been stained with hematoxylin and eosin and Van Gieson stains. The wall of the abscess is composed of necrotic debris, containing many cellular elements and merges into the surrounding brain tissue without any indication of capsule formation. The nearby brain tissue is infiltrated with mononuclear and polymorphonuclear cells which are densest about necrotic vessels and degenerating areas of brain tissue. Numerous engorged vessels are seen at the periphery of the abscess wall and a variety

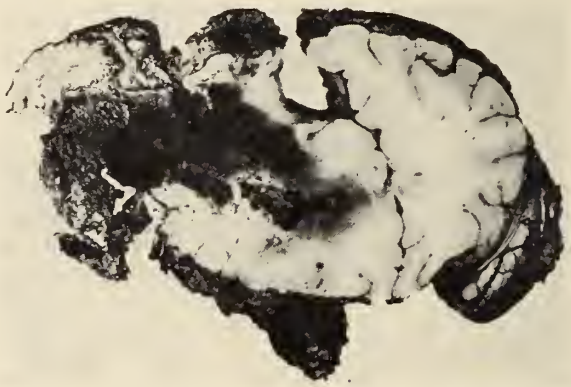

FIG. 1. Case 1. Herniating necrotic brain tissue and abscess cavity (right frontal lobe)

of degenerative changes may be noted in the nearby brain tissue. The van Gieson stain shows no reaction of fibrous tissue to the inflammatory process.

Comment. Dr. Globus: A patent foramen ovale is not uncommon. The first case of what was later to become known as paradoxical embolus (Zahn (1)) or crossed embolus (Rostand) was described by Cohnheim. The three features in his case were: (*a*) venous thrombosis (femoral vein); (*b*) patent foramen ovale; (*c*) embolism in the right cerebral artery. Since then it was found that such an embolus, may, in the rare instance, pass through a defect in interventricular septum. An embolus found in transit through the foramen ovale was described by Zahn and more recently by others.

This form of embolism is associated with antecedent pulmonary embolism, which is considered an essential factor in inducing the passage of embolus through the foramen ovale from the right to the left auricle.

It was pointed out by Thompson and Evans (2), that a clinically hidden thrombosis of a femoral vein is a common source of origin of such emboli. This may be the case in this instance.

A distinction is made between simple or infected emboli. The most common form (80 per cent) of paradoxical emboli are of the non-infectious type (origin in femoral vein). In this case, however, the subsequent surgical intervention in the brain does not permit the identification of the non-infectious or infectious character of the embolus.

Reported by *M. Sapirstein, M.D.*

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Case 2. Amaurotic Family Idiocy

[*From the Pediatric Service of Dr. Bela Schick*]

History (Adm. 421632; P.M. 11135). A baby girl, 11 months of age, was admitted to the hospital on March 20, 1938 because of cessation of progressive development. She was an only child of Jewish parents. There was no record in the family of previous instances of impaired physical or mental development and no history of parental consanguinity. Birth had been normal and postnatal development progressed in an apparently normal manner until the age of eight months. At that time the parents noticed that the child seemed weak. During her tenth month of life she made some fairly successful attempts to sit up with assistance. She would play with toys but she made no attempt to utter words. Two weeks before admission she began to cut her first teeth (the two lower incisors).

Examination. The child was plump and appeared to be well-developed. Her eyes would not follow hand motions or light. The fundi showed generalized pallor; the discs were pale, the left more than the right. In each macula region there was an area about one-third the size of the disc consisting of a brownish-red central area surrounded by a brilliant white halo.

Laboratory Data. Blood: hemoglobin, 87 per cent; red blood cells, 5,160,000 per cubic millimeter; white blood cells, 12,800 per cubic millimeter (polymorphonuclear leucocytes, 38 per cent; lymphocytes, 58 per cent; monocytes, 4 per cent). The blood Wasserman reaction was negative. The bone marrow obtained by puncture was normal. Blood chemistry: cholesterol, 405 mg. per cent; esterfield, 235 mg. per cent (difference, 170 mg. per cent); albumin, 5.9 mg. per cent; globulin, 1.8 mg. per cent; (total proteins, 7.7 mg. per cent) phosphorus, 5.7 mg. per cent; calcium, 11.6 mg. per cent; phosphatase, 26 King-Armstrong units per cent. The total fat was 1600 mg. per cent. (During her stay in the hospital there was a tendency for the cholesterol value to fall off; but the total lipoid value increased to 1970 mg. per cent. The phosphatase value dropped to 10.5 King-Armstrong units per cent over the course of the next twelve months). The cerebrospinal fluid was clear; Pandy, negative; sugar, 75 mg. per cent; cholesterol, a faint trace; chlorides, 725 mg. per cent as sodium chloride; total protein, 30 mg. per cent; Wassermann and colloidal gold tests,

negative. Repeated urine examinations were essentially negative except for traces of albumin on two occasions.

Course. A diagnosis of Tay-Sachs disease (amaurotic family idiocy) was made. During her stay in the hospital she weathered several episodes of acute infection each with temperature elevations. There occurred bilateral otitis media during the first hospital month, a conjunctivitis during the third hospital month, a questionable aspiration pneumonia during the seventh hospital month, pharyngitis in the ninth month of hospitalization, and an acute upper respiratory infection in the twelfth month of hospitalization. Her neurological condition became slowly and progressively worse. Spasticity began to appear during the first month. By her eighth month in the hospital she could no longer raise her head and she began to have difficulty in swallowing. On January 28, 1939, about ten months after admission, electroencephalographic studies were done at the Neurological Institute. These were

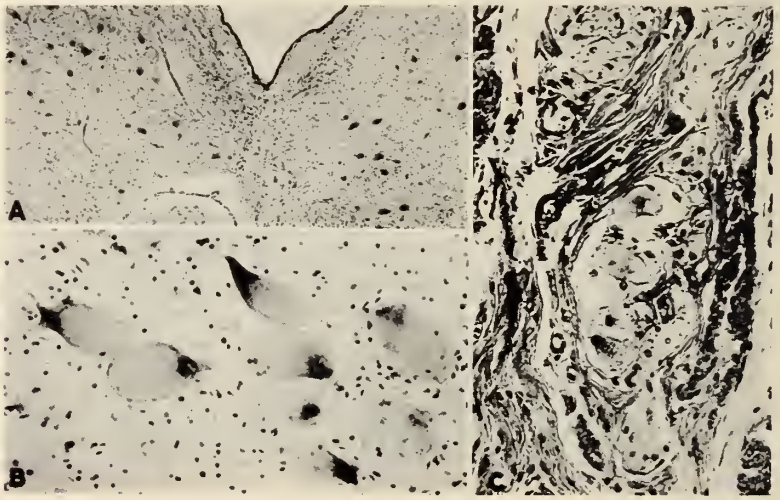

FIG. 2. Case 2. A. The lower part of the fourth ventricle showing the cell groups constituting the hypoglossal nuclei, (photomicrograph, Nissl stain).

B. Typical alterations in the nerve cells of the hypoglossal nuclei shown in Figure 2A, (photomicrograph, Nissl stain).

C. Auerbach's plexus, showing typical alterations in the ganglion cells, (photomicrograph, hematoxylin and eosin stain).

reported as showing a decreased "metabolism" wave throughout the cerebral tissues. In February, feeding by lavage had to be instituted. The following month she passed through several episodes of convulsive seizures which appeared to be of the grand mal type. Spasticity had increased progressively and the lower extremities were fixed in extension. Magnus de Kleijn reactions could be elicited. At the beginning of April, 1939 her temperature began to rise again. Respiratory difficulty set in and she died on April 13, 1939 at the age of two years after a residence in the hospital of 55 weeks.

Necropsy Findings. Brain. Gross. The skull bones were thin. There was some increase in the subarachnoid fluid. The cerebral hemispheres were markedly pale and very firm, almost rubbery in consistency. The gyri were small and narrow; the sulci were wide and deep. The optic nerves were small and very white; the optic chiasm was flat and ribbon-like. The cerebellum and medulla appeared to be rela-

tively small in proportion to the cerebral hemispheres. On sectioning the brain, a moderate symmetrical internal hydrocephalus was found.

Microscopic. Throughout the entire nervous system, central and peripheral, including the autonomic division, the nerve cells show swelling of the cytoplasm, (fig. 2 A, B, C). The cytoplasm, stained by the Nissl method, discloses an almost complete lack of Nissl substance, presenting instead a spongy reticular appearance and containing detritus like granular material; at times, the latter alone is present. In the cerebellum there is a diminution in the number of Purkinje cells and a depopulation of the internal granular layer so that the lamellation of the cortex is poorly demarcated (fig. 3A). The Purkinje cells because of their size display most clearly

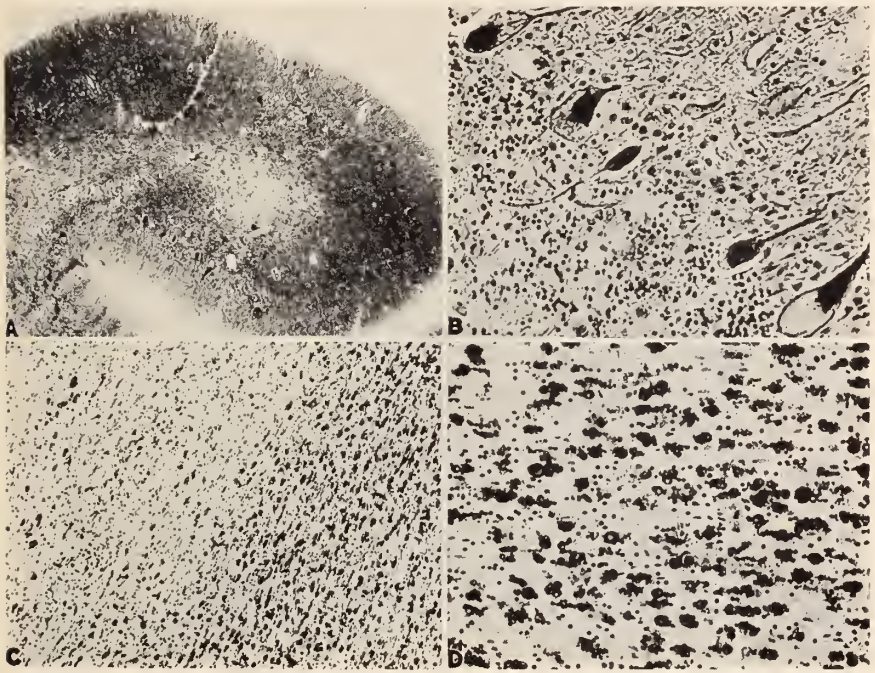

FIG. 3. Case 3. A. Cerebellar folium showing loss of Purkinje cells and the enlargement of surviving Purkinje cells, (photomicrograph, Bielschowsky stain).
B. Purkinje cells showing marked disturbance of the arrangement of neurofibrillae, (high power, Bielschowsky stain).
C and D. Fat rings and granules in cortex and subcortex indicating myelin degeneration, (photomicrograph, Scarlet Red preparation).

the internal changes of the nerve cells as seen with the Bielschowsky stain: displacement of the nucleus with an intense homogeneous staining quality; cohesion of the neurofibrillae to form thickened bands; disappearance of the neurofibrillar structure and replacement by a non-nervous reticulated structure; swelling of the cell; and the appearance of detritus-like material, (fig. 3B).

Scarlet Red preparations for fat show much more fat in the subcortex than in the cortex (fig. 3C). Furthermore, the subcortical fat is aligned in the direction of the axis cylinders, indicating active diffuse demyelinization (fig. 3D). The content of the swollen nerve cells does not stain positively for fat but often assumes a yellowish-orange tinge.

Cajal gold sublimate and Hortega preparations (Globus modification) reveal an increase in astrocytes, more marked in the subcortex. Many are fibroblastic; many show degenerative changes such as clasmatodendrosis; and many show vacuoles in the cytoplasm (degeneration or phagocytosis?).

Comment. Dr. Globus: The clinical features and course in this case of Amaurotic Family Idiocy are typical of the Tay-Sachs form of this disease. Histologically the cell changes are also typical in every way. There is, however, one deviation from the usual anatomical alterations as revealed by histo-chemical studies; it is the marked liberation of free fat in the subcortex indicating advanced and widespread demyelinization.

Reported by *J. Friedman, M.D.*

Case 3. Necrotizing Encephalitis

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

History (Adm. 440593; P.M. 11195). A boy, 7½ years of age, was admitted to the hospital on May 17, 1939. Five years previously he had fallen, striking the back of his head. There were no apparent sequelae and except for attacks of mumps and measles, he was well until three weeks before admission to the hospital, when he suddenly experienced a bout of vomiting. This ceased and he was then apparently well until one week before admission when persistent vomiting set in together with persistent frontal headache of increasing severity and attacks of abdominal pain. He became irritable and it was noticed that he would be drowsy and listless by day, but restless at night. Examination by a neurologist five days before admission disclosed a slow pulse and an unsteady gait with almost complete loss of ability to accelerate. The optic discs showed changes suggestive of papilledema. There was a slight nystagmus on right lateral gaze. There was hyperreflexia in the right extremities with a positive Babinski sign and the right abdominal reflexes were diminished.

Examination (on admission). The patient was listless, irritable and uncooperative, but oriented and rational. Pulse rate, 68 per minute. Temperature 99°F. He walked on a broad base and there was ataxia of the trunk. The physical signs showed progression and now included definite blurring of the left disc, occasional nystagmoid jerks on left lateral gaze, a mimetic facial weakness on the right side, an unsustained ankle clonus bilaterally, and bilateral Babinski signs. The outstretched right upper limb failed to maintain its position; the left one assumed a cerebellar position. There were no confirmatory cerebellar signs (ataxia, dysdiadochokinesis) in the upper or lower extremities.

Laboratory Data. Urinalysis, blood examination, and X-ray examination of the skull were all reported as normal. The blood Wassermann reaction and Kahn test were negative.

Course. A provisional diagnosis of tumor of the vermis was made. Four days after admission, the patient was subjected to ventriculography. A brain needle, inserted through the trephine openings on either side, obtained only a few drops of

slightly cloudy fluid. It was thought unwise to introduce air under these conditions and the procedure was terminated. The findings indicated that, at least, there was no internal hydrocephalus. The possibility of some type of inflammatory condition was then proposed. A lumbar puncture yielded clear cerebrospinal fluid at an initial pressure of 180 mm. of water; Ayala index, 3.3; cells, 100 per cu. mm., chiefly lymphocytes; colloidal gold curve, 2222 111 00000; Wassermann reaction was negative.

Weakness and spasticity of the right upper extremity appeared and rapidly progressed into a right hemiplegia. The patient's vomiting persisted. Papilledema now appeared in the right disc; all the superficial reflexes disappeared, and the patient began to yawn frequently. His temperature rose to 101°F. and for the duration of his illness varied between 99°F. and 102°F. His pulse rate varied irregularly between 56 and 120 beats per minute with little, if any, correspondence to the temperature variations. Once or twice a day, he began to experience episodes beginning with a sensation of falling followed by tonic and clonic seizures usually right sided but occasionally generalized. The episodes usually did not last more than a minute and

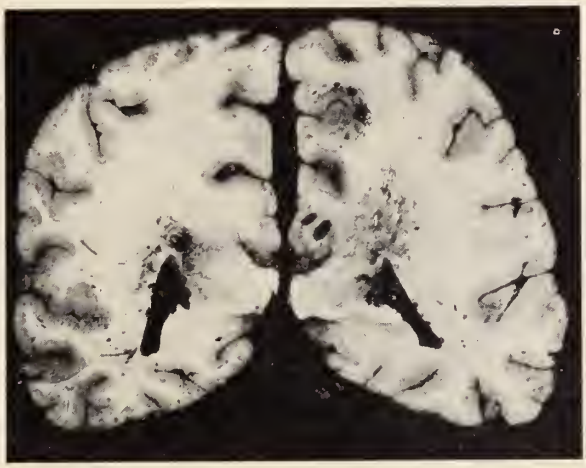

FIG. 4. Case 3. Marked discoloration of the subcortex in both occipital lobes, the main seat of the disease process.

would occur once or twice a day. Consciousness was retained at all times. A left hemiparesis now set in and the patient began to experience frequency of urination and occasional incontinence. Three weeks after admission, a pneumoencephalography was performed. There was no gross abnormality in the ventricular system but the intraventricular system was somewhat bowed to the right and the subarachnoid channels on the right were somewhat more distinct than those on the left. These findings were considered somewhat suggestive of a left sided lesion. Cerebrospinal fluid, obtained by lumbar puncture, on several occasions showed each time an initial pressure of 120 mm. of water. The Pandy test was regularly positive and the fluid contained between 10 and 17 white cells per cubic millimeter. The convulsive attacks increased in frequency. Sulfapyridine therapy was instituted. Swallowing became difficult. The patient's pupils became fixed to light and his eyes deviated to the right; rapidly progressive blindness was setting in. At this time there was bilateral papilledema with an exudate on the right nerve head. Within 24 hours he was completely blind and he died suddenly one day later, seven weeks after the onset of his illness.

Necropsy Findings. Brain. Gross. Except for a flattening of the convolutions of the cerebral hemispheres and a voluminous appearance, the brain superficially appeared to be normal. On sectioning the brain, a bilateral symmetrical yellowish discoloration was seen in the subcortex (fig. 4). It was most marked in the occipital lobes, diminishing in intensity rostrally. The discolored subcortical tissue was extremely soft to the touch and in the occipital lobes was almost liquid in consistency. The corpus callosum was discolored but felt firm.

The aqueduct of Sylvius was small and narrow rostrally but wide in its caudal part.

Microscopic. Sections taken from various regions of the brain and stained by the usual neurohistologic methods disclose widely disseminated inflammatory lesions

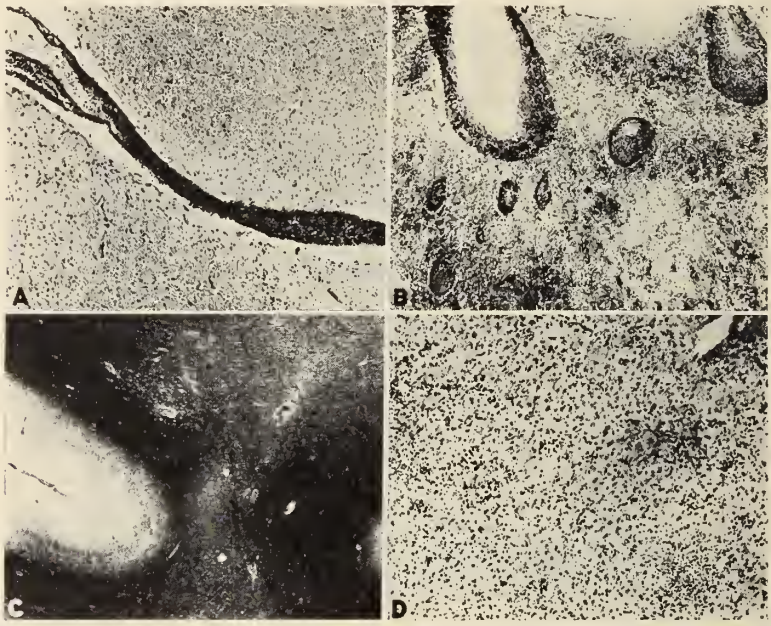

Fig. 5. Case 3. A. Intergyral meningeal infiltration with small round cells, (photomicrograph, hematoxylin and eosin stain).

B. Perivascular and interstitial accumulations of small round cells, (photomicrograph, Nissl stain).

C. Focal area of demyelinization in subcortex, (photomicrograph, Weil stain).

D. Numerous small fatty globules, (photomicrograph, Scarlet Red stain).

(fig. 5A), with most marked changes and necrosis in the region of softening described grossly. There is no evidence of neoplastic disease. Blood vessels in the region of marked softening display all stages of perivascular inflammation with degeneration and obliteration of blood vessels (fig. 5B). The perivascular cells are chiefly mononuclears, usually of the lymphocytic type, and at times elongated. They form cuffs of varying density and diameter about the blood vessels. The cuffs of greater diameter are usually the less dense and display an interna reticulum of connective tissue fibers. The subcortical tissue in this region displays marked disorganization and necrobiotic changes with numerous inflammatory cells. About the more obliterated vessels there is scarcely any demarcation between the perivascular reaction and adjacent brain tissue. Demyelinization in the subcortex varied considerably in degree but is widespread (fig. 5C). Scarlet Red preparations disclose compound

granule cells and free-lying droplets of fat throughout the area of marked softening with no striet localization (fig. 5D). Baeterial stains diselose no organisms.

The eortex overlying the region of softening shows some glial proliferation and some infiltration by inflammatory cells in the area adjacent to the subeortex; but on the whole the architeeture and nerve cells of the cortex are well preserved. There is no perivaseular reaction in the cortex exeept in a few vessels adjaeent to the subeortex. However, it is seen about meningeal vessels both in the sulei and on the surface of the brain.

The general autopsy disclosed nothing of signifieanee.

Comment. Dr. Globus: A case with a clinical course and post mortem findings strikingly similar to those noted in this case was studied in our hospital and was reported elsewhere. In that instance as in this, the clinical picture was that of a brain tumor, and such a diagnosis had to be considered very seriously because of the presence of chocked discs, and other evidence of increased intracranial tension.

However, it would seem that an inflammatory process was not entirely excluded, as sulfapyridine therapy was employed. The widespread and intensive inflammatory process is, of course, responsible for the clinical manifestations, often considered under the name of pseudo-tumor cerebri.

Reported by *S. Margolin, M.D.*

REFERENCE

Levy, Norman A.: Neerotizing eneephalitis. Areh. Neurol. & Psyeh. 38: 775, 1937.

Case. 4 Massive Cerebral Hemorrhage, with Extension into the Ventricles and Subarachnoid Space

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

History (Adm. 439641; P.M. 11167). A woman, 50 years of age, was admitted to the hospital on April 28, 1939. She had been found lying fully dressed and unconscious on the floor of her hotel room, eight hours after the time she usually left for work. One hour later, she appeared to have regained consciousness and opened her eyes but did not speak. She was then brought to the hospital. There it was learned from her sister that during the previous eight years she had been known to have mild hypertension and had occasional swelling of both ankles. She had undergone an hysterectomy eight years before admission. During the six months preceeding her sudden illness she was found to be "nervous" and was subject to occasional flushes. This was attributed to the onset of the menopause, for her menses ceased at about that time. She was known to be left-handed.

Examination. The patient who was well-developed and obese, lay very quietly in bed, with her eyes closed. Her respirations were noisy but regular. The pulse rate was 68 per minute. The blood pressure was 140 systolic and 80 diastolic. She yawned frequently. Occasionally she would open her eyes and the eye-balls would

roll at random, from side-to-side. At times, she would display "groping" movements of the right arm and leg. She did not speak but occasionally, in response to commands, she would show her teeth and raise her right arm. The right pupil was larger than the left and was slightly irregular. Both pupils reacted promptly to light. The retinal arteries were narrowed and somewhat tortuous. There was a left, central facial paresis. The left upper limb was held in adduction and flexion. It was spastic. The left lower limb was flaccid, while the right lower was spastic. The deep tendon reflexes were increased in the left upper extremity and diminished in both lower extremities. The Hoffman and Babinski signs were elicited on both sides, with the Babinski being more marked on the left side. The abdominal reflexes were absent. Both right extremities responded to pin prick. Except for pitting edema on the dorsum of each foot there were no other general physical findings of significance.

Laboratory Data. Cerebrospinal fluid: grossly bloody with slight xanthochromia of the supernatant fluid; initial pressure, 110 mm. of water; cells, 3,000 well preserved red blood cells per cu. mm.; Pandy, 4 plus. Blood: white blood cells, 15,600 per cu. mm.; hemoglobin, 96 per cent. Urinalysis: negative.

Course. A diagnosis of hemorrhage with focal damage in the right cerebral hemisphere was made. Whether it was essentially subarachnoid or intracerebral with oozing into the subarachnoid space was not agreed upon. The possibility of a ruptured aneurysm was considered.

During the patient's stay in the hospital, neck rigidity developed. The pupils became constricted. The cerebrospinal fluid pressure increased to 190 mm. of water but the composition of the fluid remained essentially unchanged. Her somnolence persisted. The fact that the patient could be roused suggested that her condition was one of deep drowsiness rather than stupor and hence, at one time, a hypothalamic lesion was suggested. A few days after admission her temperature rose rapidly, accompanied by an increase in pulse and respiratory rates. On her eighth day in the hospital she developed pneumonia, and from then on she declined more rapidly, dying fifteen days after her admission to the hospital.

Necrospy Findings. Brain. Gross. Fluid and clotted blood filled the subarachnoid space over the occipital lobes and the dorso-lateral surface of the parietal lobes. The vessels at the base of the brain displayed slight sclerotic changes. On sectioning the brain, a hemorrhagic area was found overlying the corpus callosum for almost its entire length (fig. 6A). The underlying corpus callosum was very soft; it was grayish-pink in color and friable. At the anterior horn of the right lateral ventricle, there was a defect in the corpus callosum which brought this hemorrhagic area into continuity with the underlying lateral ventricle. This defect extended caudally for almost the entire length of the corpus callosum. Both lateral ventricles were somewhat enlarged, the right more than the left, and were filled with recently coagulated blood. The third ventricle contained a small amount of blood but the aqueduct and the fourth ventricle were free of blood.

Microscopic. Serial sections of the corpus callosum in the neighborhood of the grossly recognized defect were stained with hematoxylin-eosin, Nissl, Cajal, Mallory, Van Gieson, and Weil methods.

A myelin preparation (fig. 6B) shows clearly the break in the corpus callosum as well as softening and demyelinization in that area. It also shows extravasated blood in the longitudinal fissure and in the adjacent brain tissue.

In hematoxylin-eosin, Mallory, and Van Gieson preparations, there are noted wide areas consisting of disintegrated brain tissue, free of extravasated blood elements, and also an area composed of a mixture of softened brain tissue, partially organized blood, and free blood elements. In this hemorrhagic area there are two blood vessels (fig. 6C) with practically complete dissolution (necrosis) of their walls.

Such vessels are probably responsible for the hemorrhage. Other vessels, ranging from those with partial mural changes to those with fairly intact walls are seen traversing the hemorrhagic area.

In the zone surrounding the hemorrhagic area many congested blood vessels in various stages of arteriosclerotic change are observed. There is also widespread degeneration and rarefaction. Cajal stains show a diffuse gliosis.

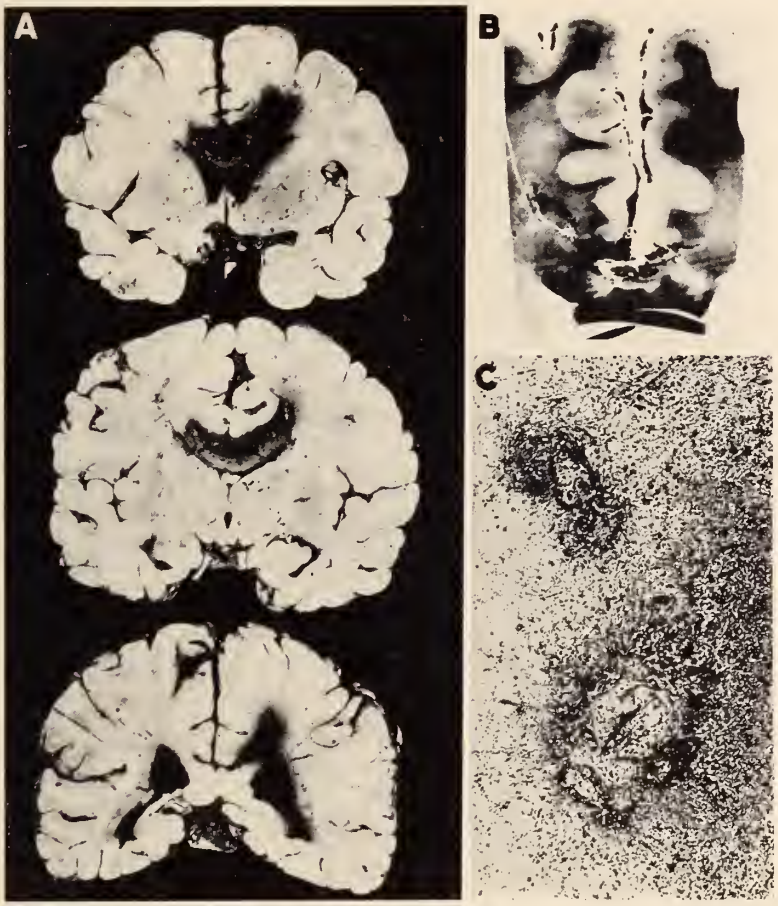

FIG. 6. Case 4. A. Coronal sections showing the hemorrhagic process affecting the corpus callosum and the overlying cerebral tissue.

B. Area including the corpus callosum showing the loss of myelin surrounding the hemorrhagic zone (Weil stain).

C. Area of encephalomalacia about necrotizing blood vessels, (photomicrograph, hematoxylin and eosin stain).

The meninges in the longitudinal fissure are thickened, distended and filled with free and partly coagulated blood. The meningeal vessels are congested and their walls are thickened. The nerve cells in the cortex are fairly well preserved in some areas, but in other areas they are swollen and in many the nuclei have shifted to the periphery of the cell. The perineuronal spaces are increased in size. In the subcortex there is a diffuse increase in glial nuclei. The blood vessels, both in the

cortex and subcortex, are congested and the perivascular spaces are enlarged. There is considerable perivascular mobilization of glia.

Comment. Dr. Globus: The pathogenesis of massive cerebral hemorrhage has been discussed repeatedly at our clinico-pathological demonstrations, and cases to illustrate the view held by us were often demonstrated. This case as previous cases shown here, gives further support to the observations that massive, spontaneous, cerebral hemorrhage is a terminal phase in a chain of events which have their origin in a more or less diffuse disease of cerebral blood vessels. It is commonly associated with generalized arteriosclerosis, advanced disease changes in the kidneys and hypertrophy of the heart.

The primary lesion leading up to the terminal and explosive hemorrhage is to be found in the gradual closing of one or more of the degenerating blood vessels. This in turn causes degeneration of surrounding tissue, and an area of softening is thus gradually being created. Vessels passing through such an area undergo disintegrating changes, though remaining patent. Such a vessel or vessels at one time or another give way at some point and hemorrhage results. The blood finds its way into the area of softening and into any other open space adjacent to the ruptured blood vessel.

Reported by *J. Schreiber, M.D.*

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.

Vagotomy plus Partial Gastrectomy for Duodenal Ulcer. A. Winkelstein and A. A. Berg. Am. J. Dig. Dis. & Nutrition 5: 497, October 1938.

After partial gastrectomy for peptic ulcer, studies in gastric secretion reveal the following:

Practically all patients with gastric ulcer at the incisura angularis develop a true achlorhydria. Of duodenal ulcer patients with high preoperative acidity only 13 per cent show achlorhydria. Of duodenal ulcer patients with low or normal preoperative acidity 70 per cent become achlorhydric.

When subphrenic anterior vagotomy is added to partial gastrectomy in the duodenal ulcers with high preoperative acidity, achlorhydria follows in a high per cent (77%).

The small number of recurrent ulcers after partial gastrectomy occur in duodenal ulcer cases with high preoperative acidity. It is, therefore, logical to advocate subphrenic vagotomy in addition to partial gastrectomy in instances of duodenal ulcer with high preoperative acidity in order to obtain an achlorhydria and thus prevent ulcer recurrences.

Coloboma of the Optic Nerve and of the Macula. A microscopic study. D. Wexler and M. A. Last. Arch. Ophth., 20: 787, November 1938.

A true congenital coloboma of the optic nerve was studied microscopically. Undifferentiated nerve and rudimentary retinal tissue partly replaced the colobomatous nerve, present at and just behind the bulbar entrance. Associated changes were: a widening of the scleral canal and the intra-dural space, displacement of the lamina cribrosa, and persistence of remnants of the hyaloid system. The choroido-macular region was also colobomatous.

Disturbed growth relationship was thought the cause of the malformations. The few pathological reports of true coloboma of the optic nerve show little correlation between the microscopic findings and the fundic appearance.

Ovarian Tumors and Diagnosis of Acute Appendicitis. P. Bernstein. Arch. Surg. 37: 1004, December 1938.

The conclusions in this paper are based upon an analysis of a large group of ovarian tumors (1,101 cases), in which 103 laparotomies were performed, after a diagnosis of acute or chronic appendicitis had been made.

Particular reference is made to the high incidence of diagnostic error in the normal, menstruating unmarried young woman who presents herself to the doctor to determine the cause of pain in the lower part of the abdomen. In this group of patients the author found an especially high incidence of ovarian pathological change, for which a diagnosis of appendicitis was made, and in which surgery was undertaken.

That disease of the ovary may simulate appendicitis, disturbances of the gall bladder or genito-urinary tract, ectopic gestation and other abdominal or pelvic conditions is well known. However, of these 103 patients operated on with a diagnosis of acute or chronic appendicitis, only four showed appendicial lesions warranting operation.

Since there is such a high incidence of diagnostic error, it is worthwhile noting the conclusion drawn from this analysis, namely that "the symptom of acute pain in the right lower quadrant of the abdomen in an unmarried female patient under thirty years of age may closely simulate appendicitis, but a painstaking history and a twenty-four hour period of careful observation will in many instances spare the patient an unnecessary operation."

End Results in Cases of Fibrosarcoma of the Extremities. E. M. Bick. Arch. Surg. 37: 973, December 1938.

The end results in twenty cases of fibrosarcoma of the extremities, followedeither to death or to a five year cure, were reported. An additional four cases, in which the five year end result has not yet been attained but in which the course so far was in complete accord with that of the major series, were added. It was concluded that in any case of fibrosarcoma of the extremities, for which complete surgical excision of a primary lesion was anatomically feasible, such treatment is indicated. When complete surgical excision is not anatomically feasible, amputation of the limb is imperative. Amputation is also imperative at the first sign of a recurrence. Irradiation, as applied up to this time, has not proved effective. Of the original twenty cases, nine died from neoplastic disease within a five year period. Eight patients (40%) were alive without sign of recurrence or metastases at the end of five years. One patient, seventy-six years old, died of pneumonia four years after primary excision with no evidence of recurrence or metastases. Another patient died of an unknown disease nine years after amputation.

Treatment of Early Measles With Convalescent Serum. J. L. Kohn, I. F. Klein, and H. Schwarz. J. A. M. A. 111: 2361, December 24, 1938.

Measles convalescent serum in small amounts can prevent or modify measles in children if given within a few days after exposure. Sporadic attempts also have been made to mitigate measles after it has reached the active stage by administering convalescent serum before, during, and after the appearance of the eruption. Most investigators have stated that these attempts were unsuccessful.

It also has been reported by many authors working on experimental virus disease that once a pathogenic virus has invaded the body cells it is impossible for a therapeutic serum to cause any beneficial effect. The etiologic agent of measles in the light of many studies is probably a virus.

Twenty-four children were injected intravenously with varying amounts of measles convalescent serum in the pre-eruptive stage of measles. Unquestionable modification of the measles was obtained in nineteen. The optimum dose was between forty cubic centimeters and fifty cubic centimeters. Fifty cubic centimeters of normal serum given to nine children gave little, if any, modification.

This type of therapy is valuable in the pre-eruptive stage of measles in debilitated children or in children sick with another illness. In this way fatal or prolonged illness due to a superimposed severe measles can perhaps be avoided.

Articular Manifestations of Meningococcic Infections. A. J. Schein. Arch. Int. Med. 62: 963, December 1938.

A complete review of the literature on meningococcic arthritis is presented, with an analysis of 23 cases from a large number of cases of meningococcic infection.

Classification is made, according to the criteria of Herrick and Parkhurst, into

three main groups: (1) the early, often premeningitic, polyarthritic or arthralgic type of involvement; (2) the ordinary postmeningitic monoarthritic type; and (3) the type resembling serum sickness. It is further pointed out that intermediary and atypical types abound. Illustrative cases are presented.

The resemblance of the pathologic and clinical picture in many cases to that of gonorrheal and other arthritic disorders is emphasized.

Whereas in the literature the prognosis is said to be uniformly favorable, with few exceptions (which are given), 3 of 23 cases are presented in which articular destruction and ankylosis eventually resulted, as well as others in which various types of orthopedic treatment were required.

The prognosis of the articular complication is much better for children than for adults.

The possible effect of recent refinements in the therapy of meningococcic infections on prognosis and prophylaxis is pointed out, especially as regards the efficacy of meningococcic antitoxin (Hoyne).

Utilization of Intravenously Injected Sodium d-Lactate as Test of Hepatic Function. L. J. Soffer, D. A. Dantes, and H. Sobotka. (With assistance of Mildred D. Jacobs.) Arch. Int. Med. 62: 918, December 1938.

By means of this test it is possible to differentiate between jaundice due to diffuse intrahepatic disease and extrahepatic obstruction. The test is dependent essentially on the fact that the normal individual is able to convert intravenously injected sodium d-lactate into glycogen completely or almost completely within thirty minutes. The retention in the blood stream of five milligrams or more of the injected lactate per hundred cubic centimeters of blood, after thirty minutes is considered abnormal. It has been shown previously by the authors that patients with obstructive jaundice of not more than a few weeks' duration, react in a normal fashion to this test, while those with diffuse parenchymal disease of the liver show a retention of more than five milligrams per cent. As a result of investigation of a limited number of diabetics, it would appear that this disease does not influence the results. The comparison of this test with the other liver function tests which are generally performed in the presence of jaundice, would seem to indicate its superior reliability from a differential diagnostic standpoint.

Hepatic Complications in Polycythemia Vera with Particular Reference to Thrombosis of the Hepatic and Portal Veins and Hepatic Cirrhosis. A. R. Sohval. Arch. Int. Med. 62: 925, December 1938.

A case of polycythemia vera is reported in which the appearance of sudden hepatic enlargement and the rapid development of ascites and jaundice were found to be due to thrombosis of the hepatic veins.

The incidence and significance of enlargement of the liver in 60 cases of polycythemia vera are discussed. Marked enlargement of the liver often signifies the presence of a complication, such as phenylhydrazine jaundice, leukemic transformation, myocardial decompensation, hepatic cirrhosis or thrombosis of the hepatic veins.

In the differential diagnosis of polycythemia vera associated with hepatic enlargement, ascites and jaundice, thrombosis of the hepatic veins is likely when there has been sudden enlargement of the liver, rapid accumulation of ascites, resistance of ascites to mercurial diuretics, frequent terminal jaundice and a markedly abnormal plasma cholesterol partition. Cirrhosis of the liver is a probability if the enlarged liver is observed to decrease in size and the ascites responds to diuretics. Ascites, hepatic enlargement, and jaundice are infrequent in complicating thrombosis of the portal vein.

Acute Bulbar Poliomyelitis Following Recent Tonsillectomy and Adenoidectomy. M. Stillerman and A. E. Fischer. Am. J. Dis. Child. 56: 778, October 1938.

Thirteen cases of acute anterior poliomyelitis which followed a recent tonsillectomy and adenoidectomy were reported. Ten of these occurred during the outbreak in 1935, the other three in a small series of cases observed during 1937.

The interval between the operation and the onset of the disease was ten to twenty-two days. It was significant that although only 10 per cent of the entire series of over 700 cases which were seen in 1935 and 1937 developed the bulbar or encephalitic type of poliomyelitis, 9 of the 13 cases which were recovering from tonsillectomy and adenoidectomy were of that type. This significantly higher incidence of bulboencephalitic forms and the time interval suggest the operative field as the portal of entry of the poliomyelitis virus. It is suggested, therefore, that tonsillectomy and adenoideetomy or other non-urgent operations about the nose and throat be postponed during outbreaks of poliomyelitis.

Clinical Criteria in Diagnosis of Carcinoma of the Female Breast. S. Richman. Miss. Valley Med. J. 61: 20, January 1939.

Experience in large tumor clinics has revealed that the average general practitioner makes frequent errors in recognition and proper evaluation of the early clini cal manifestations of cancer of the breast. Since the best results follow treatment of the early stage of caneer of the breast, it is the duty of the physician to realize the significanee of the early signs of this disease.

While it is frequently true that the exact nature of a lump in the breast can only be revealed by a histological study of a removed specimen, nevertheless, there are certain clinical manifestations which can be utilized by the physician to determine the presence or absence of cancer. These clinical criteria, such as hard consistency of the lump, skin retraction and adherence, displacement and retraction of the nipple, are discussed in detail.

In conclusion, it is stressed that every patient with a lump in her breast, irrespective of age, should have a scrupulous and complete examination of both breasts and the regional lymphatic areas. Many authorities believe that cystic disease of the breast may become the seat of carcinoma. Therefore, one should not dismiss as neurotic or cancerophobic those patients, especially when past the age of forty, who, having had a thickening or a tumor in the breast for several years, are at present even slightly suspicious that the mass has become tender or has increased in size.

Sulfanilamide in Gonorrhea. A. Cohn, A. Jacoby, B. A. Kornblith and M. Wishengrad. Am. J. Syp. Gonorrh. & Ven. Dis. 23: 41–47, January 1939.

This study is based upon the treatment of 100 cases of gonorrhea of both acute and chronic types. The treatment consisted of the oral administration of 5.3 Gm. of the drug in divided doses for four days and then 2.6 Gm. daily for seven additional days. In children, the dosage was computed at 0.09 Gm. per kilo. All of the patients suffered slight toxic effects. The treatment was given to ambulatory patients. Cures as shown by the absence of symptoms, negative smears and cultures, and negative smears following provocative measures were obtained in 55 per cent of the cases.

The concentration of sulfanilamide in the blood showed no consistent relationship to good or unfavorable therapeutic results. Some cases with high concentration showed some toxic phenomena and were nevertheless resistant to this form of therapy. An average of five days was necessary for the complete disappearance of ingested sulfanilamide from the blood. In some cases, this may not occur for twelve days.

Sulfanilamide therapy should show results in the elimination of organisms and the

elimination of discharge in four days. If such a result is not obtained, the case is considered resistant and other forms of therapy should be instituted inasmuch as continued use of the drug will yield no further favorable effect.

Hematometra. Bernstein and Walters. J. Obst. & Gynec. 37: 126, January 1939.

The subject of hematometra is considered from the standpoint of etiology, pathology and treatment. An interesting group of cases representing various causes of this rare condition is presented.

The incidence of this condition among all gynecological admissions to The Mount Sinai Hospital over a period of twenty years was found to be 0.1 per cent.

Hematometra is due either to congenital or acquired atresia. Blood retention incidental to menstruation or other bleeding produces distention of the vagina (hematocolpos), uterus (hematometra), and Fallopian tubes (hematosalpinx). Hematovarium and hematoperitoneum also occur.

The most frequent cause of hematometra is the congenital imperforate hymen. The acquired causes are due to childbirth injuries and post-partum infections.

The pathogenesis involves the collection of blood in the genital tract above the site of obstruction. The blood is dammed back into the peritoneal cavity in some cases, and may distend the entire tract to paper thin consistency.

In one case only was an estrogenic reaction present (personal communication of Robert T. Frank).

In children, the diagnostic triad is an imperforate bulging hymen, a pelvic tumor, and delayed menses.

In adults, diagnosis is not as simple, since the gynatresia is usually acquired and partial. Large hematometra are therefore rare.

Treatment is always surgical. Conservatism is advocated.

The author believes that since drainage from below is most often effective in our experience it is always indicated first in the absence of clinically infected hematosalpinges. However, the patient should be carefully observed for complications.

Laparotomy is necessary only if serious complications, such as hemorrhage, peritonitis, and tubo-ovarian abscess are present, and drainage is advisable in these cases. In older women, especially at the climacterium, radical measures were more reasonably utilized, since benign, and malignant tumors often found complicating the hematometra necessitated panhysterectomy; infection, often present, required adequate drainage.

X-ray Demonstration of Submucous Myomas by Combined Use of Hippuran and Carbon-Dioxide Injection. I. C. Rubin. Am. J. Obst. & Gynec. 37: 75, January 1939.

The presence of submucous myomas can be diagnosed roentgenologically by the intrauterine injection of hippuran followed by CO_2. Neither by itself is adequate for this purpose. The hippuran is used in concentrations of 80 to 100 per cent which, when expelled from the uterine cavity, leaves a crystalline deposit on the uterine mucosa and the mucosa covering the submucous tumor. The injection of CO_2 serves as a transparent contrast to the densely opaque hippuran outline. Both media are innocuous, each being well tolerated by the organism. There is no irritation and no residue or foreign body reaction. In selected cases where recognition of submucous myoma is important from the viewpoint of the choice of therapy, this method appears to be serviceable.

Objections to the Use of Kirschner Wire for Fixation of Femoral Neck Fractures. S. Selig. J. Bone & Joint Surg. 21: 182, January 1939.

Impressed by the work of Telson and Ransohoff, the author used Kirschner wires for the fixation of fourteen intracapsular fractures of the neck of the femur. Because of the lack of strength and their tendency to wander deeply into the tissues, more rigid devices are now used.

Two illustrative cases with X-rays are cited to demonstrate the bending of the wires on weight bearing and their tendency to wander into the pelvis. Although the wandering tendency can be overcome by threading the wires and the use of fixation nuts, the use of a stronger, more rigid device is desirable.

Vitamin Therapy in Ophthalmic Practice. J. Laval. Am. J. Ophth. 22: 33, January 1939.

The article first reviews our knowledge to date of the actions of vitamins A, B, C, and D. The results of various experiments with these vitamins by different workers in this field are also reviewed. Experiences of the ophthalmologists with vitamins in certain ophthalmic conditions are re-capitulated and the following suggestions are made:

(1) Vitamin A—Prescribe a tablespoonful of cod liver oil twice daily in cases of poor dark adaptation, phlyctenular kerato-conjunctivitis, photophobia, and low-grade conjunctivitis in women who are on a slenderizing diet or in cases of other corneal and conjunctival lesions in which the history shows a lack of vitamin A intake.

(2) Vitamin B (B^1 and B^2)—Prescribe eight yeast tablets daily of the Brewers'-yeast type, or prescribe the powdered form. This is to be used in cases of incipient cataract, in optic neuritis, retrobulbar neuritis, and also in toxic amblyopia.

(3) Vitamin C—Order the juice of at least two large oranges or one grapefruit daily in cases of incipient cataract. (This is in addition to the Brewers' yeast which is also to be taken daily.) In cases of intra-ocular hemorrhage order the juice of four lemons daily.

The Role of Sweat as a Fungicide. S. M. Peck. Arch. Dermat. & Syphilol. 39: 126, January 1939.

Thermal sweat may have fungistatic and fungicidal properties at a pH below 7. Concentrated heat sweat is fungistatic even when alkalinized. The fungicidal properties of sweat are due to its content of acetic, propionic, caproic, caprylic, lactic and ascorbic acid. These substances must be present in the proper concentration to exert a fungistatic or fungicidal effect. There seems to be a relation between the localization of fungous infection and the distribution of sweat on the surface of the body. Areas which are exposed to the greatest concentration of sweat seem to have less tendency to fungous infection. Sebum, as exemplified by the contents of a sebaceous cyst, could not be shown to be fungicidal or fungistatic. Topical applications of ingredients of sweat, such as mixtures of lactic acid, propionic acid, butyric acid and ascorbic acid in proper concentrations, have proved valuable in the treatment of fungous infections.

Plethysmographic Studies of Peripheral Blood Flow in Man; Criteria for Obtaining Accurate Plethysmographic Data. D. I. Abramson, H. Zazeela, and J. Marrus. Am. Heart J. 17: 194, February 1939.

Plethysmographs for measuring blood flow by the venous occlusion method in the hand, forearm and foot are described. The various pitfalls associated with the plethysmographic determinations of blood flow in the extremities are presented. The criteria used to recognize and eliminate artifacts in the record are discussed.

Physiologic Factors Affecting Resting Blood Flow in the Extremities. D. I. Abramson, H. Zazeela, and J. Marrus. Am. Heart J. 17: 194, February 1939.

The various physiologic factors which may modify normal resting blood flow determinations are discussed, and methods for obviating them are presented.

The normal ranges of blood flow values for the hand, forearm and foot are presented in tabular form for different states of vasomotor control and their significance is discussed.

Regional Ileitis. B. B. Crohn. Surg., Gynec. & Obst. 68: 314, February 1939.

This most recent paper on regional ileitis discusses some of the more recent debatable points in the life history of the disease. It decries the restriction of ileitis to persons of Jewish heritage; it questions the influence of trauma. There is little new information regarding etiology.

In the pathology of the disease "skip-areas" are presented by diagrams; the unfortunate overlooking of these "skip-areas" as a cause of post-operative recurrence is emphasized.

The fistulous tracts resulting from a leaking or ulcerating loop of terminal ileum sagging into the pelvis are discussed. The probable course and continuity of such tracts to the perineal surface are conjectured.

Medical treatment is still disparaged; a 10.5 per cent operative risk is conceded and unfortunately it is admitted that recurrence takes place in 7.7 per cent of resected cases.

Mechanism of Localization of Vegetations of Bacterial Endocarditis. A. Allen. Arch. Path. 27: 399, March 1939.

An attempt is made to account for the remarkable selectivity of the localization of vegetations of bacterial endocarditis on the basis of two components of hemodynamics; namely, impact and contact. It is suggested that these same principles are a common and major denominator of the following basic facts: (1) The susceptibility of fibroplastically deformed rheumatic valves; (2) the greater occurrence of bacterial endocarditis on the left side of the heart; (3) the predisposition of congenital lesions; (4) the relative rarity of bacterial endocarditis in fibrillating hearts.

Clinical Experiences with Sulfanilamide Therapy. R. Ottenberg. New York State J. M. 39: 418, March 1939.

The article reviews the clinical experience in about 200 hospitalized cases. It especially stresses the dangerous idiosyncracies, such as acute hemolytic blood destruction and agranulocytosis which make it advisable to use the drug with caution in diseases which are of themselves not serious.

Gross Hemorrhage as a Complication of Peptic Ulcer. B. B. Crohn and H. H. Lerner. Am. J. Dig. Dis. 6: 15, March 1939.

This paper is a natural sequence to a paper published some years ago. The original paper covered a period from 1915 to 1925 in the medical wards of the Hospital. The present paper covers the period from 1926 to 1938. The mortality figures quoted in 1925 were 4.2 per cent; the present mortality figures are higher, namely 6.5 per cent.

There were no deaths under the age of 35, no deaths seen in women, and no deaths from gastro-jejunal ulcer.

The advantages of Meulengracht's diet are seriously questioned, particularly during the active early stage of hemorrhage. Large transfusions are decried and even small transfusions and intravenous infusions should be witheld and administered only in great urgency.

The urea values are not sharply indicative of prognostic significance, the rise of urea appearing as an indication of shock rather than of extent of hemorrhage.

Urgent operation for bleeding ulcer in the first few days is discussed, but not truely advocated, while on the other hand, indication for operation upon repeated hemorrhage in patients over 45 years of age is clearly recognized.

Parathyroidectomy for Raynaud's Disease and Scleroderma; Late Results. A. R. Bernheim and J. H. Garlock. Arch. Surg. 36: 543, March 1939.

The authors, as a result of their experience, have come to the conclusion that the operation of parathyroidectomy has no place in the therapy of Raynaud's disease. While the immediate results are impressive and often dramatic, the late results do not measure up to the expectations expressed in our original paper. However, in the treatment of scleroderma, whether the condition is generalized or confined to the hands and face, they are of the opinion that parathyroidectomy offers the patient the probability of recession of the disease in the early stages, and of halting of the process in the late ones. At present, no other method of treatment is known to them which offers this outlook to the patient suffering from scleroderma.

BOOK REVIEW

M. Benmoschĕ, M.D. A Surgeon Explains to the Layman. Simon and Schuster, New York, 1940.

This is a book of simple, accurate information for the lay reader, especially as it relates to diseases usually treated by operation. It also clearly describes the surgical aspects of each disease in a manner resembling that of the newspaper articles of recent years written for the information of the public.

Dr. Benmoschĕ has selected as his subject the more frequent types of illness and injury, and he addresses the Man-in-the-Street and his Wife, who would find it difficult to gain the desired knowledge except in a medical library and even then only with the aid of one accustomed to this form of investigation.

The language is delightfully colloquial, and each subject, while not discussed in minute detail, presents enlightening information.

The book gives to the layman valuable and authoritative knowledge; it is not at all intended for the surgeon.

Line illustrations, diagrammatic in character, contribute much to the easy comprehension of the entire subject.

The writer of this book review predicts a wide and well-deserved circulation of the volume.

Howard Lilienthal, M.D.

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THE CONTINUOUS INTRAVENOUS ADMINISTRATION OF MORPHINE AFTER OPERATION

HAROLD NEUHOF, M.D.

[*From the Surgical Service of Dr. Harold Neuhof*]

This study of an undescribed method of postoperative administration of morphine is based on the principle of slow intravenous therapy, established by means of sodium citrate in 1921,[1] applied subsequently to other drugs, and spectacularly to the chemotherapy of syphilis.[2]

Morphine is the sovereign remedy for postoperative pain or discomfort. Prompt relief generally follows a substantial hypodermic dose. Relief often is followed within a few hours by restlessness, discomfort, or pain, and one or more repetitions of the dose may be required. Undesirable features of hypodermic morphine therapy which are noted at times may be summarized as follows: (1) An extreme immediate effect. (2) Too short a period of relief. (3) Considerable restlessness, discomfort, or pain between doses. (4) A more or less stuporous state when too frequently given. (5) Undue strain on the operative field because of restlessness, if administered too infrequently. (6) Idiosyncrasies.

In order to obviate the undesirable features which may and often do accompany the customary therapeutics of morphine, and in order to obtain a more desirable and uniform pharmacological action, the drug has been administered in continuous intravenous saline solution after a variety of major operations. The latter have consisted of cases in which considerable postoperative pain and restlessness could be anticipated. The method also has been applied after less capital operations in selected instances. The procedure may be outlined as follows: Adult patients usually receive a hypodermic dose of morphine (gr. $\frac{1}{4}$) before operation. The intravenous administration of normal saline solution as a slow drip containing morphine sulphate is begun immediately after operation. For adults the dose per hour is a sixteenth of a grain of morphine sulphate in 100 cc. of saline solution. The solution is prepared by adding 2.5 cc. (gr. $\frac{5}{8}$) of a standard morphine solution to 1000 cc. of normal saline solution. One hundred cubic centimeters of this solution are given every hour. If required for

[1] Neuhof, H., and Hirshfeld, S.: The Slow Intravenous Administration of Large Doses of Sodium Citrate. New York M. J. 113: 95 (January), 1921.

[2] Chargin, L., Leifer, W., and Hyman, H. T.: Studies of Velocity and Response to Intravenous Injections: Application of Intravenous Drip Method to Chemotherapy as Illustrated by Massive Doses of Arsphenamine in Treatment of Early Syphilis. J. A. M. A. 104: 878 (March), 1935.

complete relief of pain or restlessness, the amount of solution can be stepped up to 150 cc. per hour, thus administering approximately grain $\frac{1}{10}$ morphine per hour. As a precaution against error, the flask containing the morphine in saline solution is tagged with the patient's name. The intravenous medication of morphine has usually been given for 24 to 36 hours. Thus the total amount of morphine administered has ranged from approximately $1\frac{3}{4}$ to $2\frac{1}{2}$ grains.

The results have been noteworthy in respect to the uniformity and extraordinary efficacy of action of the drug when administered in the foregoing manner. Without additional medication, there has been continuous and complete freedom from pain or discomfort as well as a state of well being otherwise rarely seen after major operations. In some instances the absence of any symptoms referable to the operative field has been truly remarkable. The absence of drowsiness or torpor referable to morphine has been surprising. There has been no undue retention of urine, abdominal distension, or difficulty with bowel movements, which might have been referable to morphine. The whole picture has been in striking contrast to that seen so often after the customary administration of morphine.

Both the duration of administration and the dosage have been set arbitrarily. Larger doses probably would be safe and smaller doses might suffice. The dosage for children has been based approximately on age. In no instance has there been a suggestion of morphine poisoning. At times the respiratory rate is slowed even in the first hour—an unexpected phenomenon in view of the amount of morphine (gr. $\frac{1}{16}$) administered in that period. The respiratory rate should be frequently observed and the morphine solution discontinued for a time if respirations are too greatly slowed. Idiosyncrasies to morphine have not been noted, perhaps because only exceedingly minute amounts of morphine enter the circulation at any one time. Since the administration of intravenous fluids after a great variety of operations is recognized generally as good practice, the use of a moderate quantity of saline solution as a vehicle for morphine should be acceptable. Larger amounts of saline solution than 100 cc. per hour or varying amounts of glucose solutions can of course be given when indicated.

This method of administering morphine is advocated here for the immediate and early postoperative period. It may be prolonged beyond the first two days for special reasons, as in cases of peritonitis. The method also can be employed whenever the combination of a uniform administration of morphine with intravenous fluids is desired, as in thyrotoxicosis, the preoperative or postoperative management of severe Graves' disease, severe acute colitis, or peritonitis. As established by experiments and by clinical experiences with sodium citrate, the principle can be applied as well to the administration of other intravenously suitable drugs when a uniform and continuous effect is desired.

REIMPLANTATION OF THE URETER INTO THE RENAL PELVIS

Treatment of the Postoperative Valvular Obstruction by Cystoscopy Through the Nephrostomy Sinus

A. HYMAN, M.D. and H. E. LEITER, M.D.

[*From the Surgical Service*]

The opportunities for reimplanting the ureter into the renal pelvis are rare. Such occasions may arise in instances of severe stenosis or stricture of the uppermost part of the ureter or ureteropelvic junction, especially when associated with high insertion of the ureter into the pelvis or where the obstruction at the ureteropelvic junction is caused by an aberrant renal artery which, if resected, would result in a large area of renal infarction. This operation may also be applicable to cases of accidental avulsion or severance of the upper end of the ureter (1). The rationale of this procedure is to conserve a fairly satisfactory organ which would otherwise be subjected to a nephrectomy.

Kuster (2) performed a ureteropyeloneostomy as far back as 1891. Quinby (3) in 1929 reported in abstract seven cases in which this operation was done for hydronephrosis. In each, the obstruction was apparently associated with an aberrant artery. He was of the opinion that simple division of the aberrant artery, even if the loss of its blood supply to the kidney seems of no moment, is by no means so direct an attack on the problem as ureteral reimplantation, combined if necessary with resection of the redundant portion of the pelvic wall. There was no mention of the pyelographic results. In his case "4", reported in 1929, cystoscopic examination revealed good function of the operated kidney. In the discussion, Moore (4) expressed the opinion that infection should be cleared up before a plastic operation is performed; and Eisendrath (5) quoted a case operated upon by Koll in which an aberrant artery was ligated, only to be followed by necrosis and suppuration of that part of the kidney. Von Lichtenberg (6) in the same year reported three cases of ureteropyeloneostomy, once for a congenital abnormality and twice for stricture of the ureteropelvic junction. Walters (7), in 1933, also reported three cases of ureteropyeloneostomy. In one patient with a hydronephrosis due to aberrant vessels which were too large to cut, an accurate anastomosis of mucosa to mucosa was done over a catheter splint. The postoperative excretory urograms showed a decrease in the hydronephrosis. In his two other cases, secondary operations were necessary to remove a valve-like portion of ureter which obstructed the ureteropelvic junction. He emphasized the im-

portance of an accurate anastomosis. Lubash (8) described a novel operation for the reimplantation of the ureter with the idea of avoiding such valve formation.

The following case is presented to show a late successful end-result of ureteropyeloneostomy as revealed by comparison of preoperative excretory urograms with those taken more than seven years later. We wish to reemphasize the importance of accurate anastomosis to avoid valve formation and to present the novel manner in which this valvular obstruction was overcome in this patient by cystoscopy and fulguration of the valve through the nephrostomy sinus.

CASE REPORT

History (Adm. 409635). A. D., a woman, aged 45 years, was first admitted to the hospital on April 20, 1928 complaining of pain in the right loin. At this time she admitted knowledge of having had hypertension for five years. Her father died of apoplexy at 68 years of age and her mother died of natural causes at 75 years of age. Her present illness began three and a half months prior to admission with burning on urination, pyuria and hematuria. This was followed by severe pain in the left loin. Shortly thereafter she was cystoscoped at another hospital, but no treatment was advised or given. Following cystoscopy, pain appeared in the right loin.

Examination. There were few abnormalities to be noted. The fundi were normal. The right kidney was palpable and tender.

Laboratory Data. The hemoglobin was 72 per cent. The blood pressure was 133 systolic and 80 diastolic. Her urine showed a specific gravity of 1024, no albumin, only a few white blood cells on microscopic examination and a culture revealed B. coli. The phenolsulphonphthalein test showed 60 per cent excretion in four hours. The blood urea nitrogen was 12.0 mg. per cent. A plain roentgenogram of the urinary tract was normal.

Cystoscopy and Pyelography. Indigo carmine given intravenously appeared from both sides within five minutes. Both ureters were catheterized without obstruction. The capacity of the right renal pelvis was 11 cc. and that of the left was 50 cc. The right pyelogram showed a slight degree of hydronephrosis while the left showed a marked degree of dilatation (fig. 1).

Course. The patient refused operative interference and was discharged from the hospital against advice. She was readmitted to the service of the late Dr. Leo Kessel, on September 3, 1932 because of the increasing frequency of attacks of pain in the left loin during that year. At that time she showed distinct evidences of hypertensive retinopathy. Her blood pressure was 222 systolic and 120 diastolic. Excretory urography demonstrated good excretion of the dye from the right kidney, which was only slightly dilated. The left kidney showed diminished excretion and the pelvis was enormously dilated (fig. 2).

Cystoscopy and Left Retrograde Pyelography. Indigo carmine appeared from both sides six minutes after intravenous injection. Both ureters were catheterized. The right renal pelvis contained 30 cc. of urine and the left renal pelvis contained 45 cc. Left pyelogram revealed a well marked hydronephrosis with the dye still trapped in the roentgenogram taken fifteen minutes later. She was transferred to the service of the late Dr. Edwin Beer where she was operated upon by Dr. A. Hyman.

Operation. Through a lumbar incision under spinal anesthesia, the left kidney was exposed. It was twice the normal size with an extrarenal pelvis almost 6 cm. in diameter. There were evidences of periureteritis and a small aberrant vessel

which crossed the ureteropelvic junction was then severed. Following this procedure it was still impossible to express the contents of the distended pelvis into the ureter. The pelvis was then opened and it was found that a fine probe could barely be passed down into the ureter, due to a marked narrowing of the uppermost 2.5 cm. of the ureter. The lower 2 cm. of the pelvis were then resected together with the upper stenosed 2.5 cm. of the ureter. The renal pelvis was then closed with fine catgut sutures after passing a number eight French soft catheter through the renal parenchyma into the pelvis. The lower end of the catheter had five openings. It was then passed down the upper end of the ureter for about 5 cm. The upper end of the ureter was then tied with catgut so that it was attached to the catheter. The catheter with the attached ureter was then drawn up into the reconstructed pelvis so that approximately 2.5 cm. of the ureter projected into the pelvis. The anastomosis was then reinforced with a few fine catgut sutures. Part of the free catheter within the renal pelvis had openings which permitted the catheter to act as a nephrostomy tube as well as a splint for the anastomosis. The wound was then closed in the usual manner.

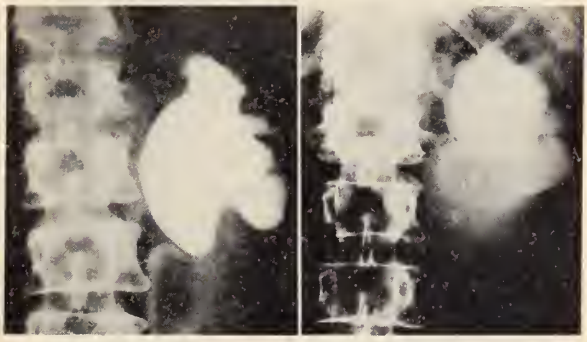

FIG. 1 FIG. 2

FIG. 1. (Left) Left ureteropyelogram taken April 26, 1928, showing marked stenosis of upper ureter with moderate hydronephrosis.

FIG. 2. (Right) Intravenous pyelogram taken September 8, 1932, showing marked dilatation of left renal pelvis and calyces.

Postoperative Course. Following the operation the patient improved steadily. The nephrostomy tube drained well. Eleven days after the operation the bladder (right kidney) urine contained 0.2 per cent urea nitrogen and the left kidney drainage contained 0.35 per cent urea nitrogen. Four days later when indigo carmine was introduced through the nephrostomy tube it appeared immediately in the bladder urine. The patient was then given 1 cc. of phenolsulphonphthalein intramuscularly. The right kidney excreted 50 per cent of the dye after four hours, while the left kidney excreted only 10 per cent after the same length of time. The catheter splint and nephrostomy tube were then withdrawn for 5 cm. so that the end was outside of the ureter but still remained within the renal pelvis. Three days later when indigo carmine solution was again introduced through the nephrostomy tube into the left renal pelvis the dye failed to appear in the bladder urine even after one and a half hours. The patient was then cystoscoped and a ureter catheter was passed up the left ureter into the pelvis without encountering any obstruction. The ureter catheter was made indwelling. The nephrostomy tube was clamped so that all the urine from the left kidney drained through the ureter catheter. A few days later the

ureter catheter was pulled out for several centimeters so that its upper end was about in the mid-ureter. It failed to drain and the patient developed left lumbar pain which was relieved by unclamping the nephrostomy tube. After another month of treatment with indwelling left ureter catheters and irrigations of the renal pelvis without relief of the apparent ureteropelvic obstruction it was decided to send the patient home with the nephrostomy tube.

Second Admission. She was readmitted to the Surgical Service on January 9, 1933 complaining of pain in the left hypochondrium. Her blood pressure was 170 systolic and 90 diastolic. Phenolsulphonphthalein given intramuscularly showed an excretion of 47 per cent from the right kidney and 20 per cent through the left nephrostomy tube. Roentgen-ray examination revealed the outlined pelvis and calyces but no opaque material was seen either in the left ureter or in the bladder region (fig. 3). In view of the apparent obstruction at the ureteropelvic junction

FIG. 3. Showing nephrostomy tube in situ

which prevented fluid in the pelvis from running down into the ureter but permitted a catheter to pass readily up the ureter into the pelvis, it was felt that a mucous membrane fold might be acting as a valvular obstruction. In order that the ureteropelvic junction might be visualized without the patient being subjected to another operation she was cystoscoped through the nephrostomy sinus under gas-oxygen anesthesia. A number twenty-four French Brown-Buerger operating cystoscope was used. A mucous membrane fold was visualized on the posterior side of the ureteropelvic junction and it was sickle-shaped in appearance. This fold was electrocoagulated. Because of the presence of purulent urine from the left kidney the nephrostomy tube was allowed to drain continuously for the next twenty days. The tube was then clamped. The patient did not develop pain in her left side as she had previously experienced and her temperature remained normal. The nephrostomy tube was removed and within twenty-four hours the lumbar sinus stopped draining urine. The patient was discharged from the hospital on March 4, 1933.

Follow-up Data. November 17, 1933: Cystoscopy was performed and showed the bladder urine to be clear. Both ureters were catheterized to the kidney pelvis without obstruction. There were 12 cc. of urine within the right kidney pelvis and none

in the left pelvis. Indigo carmine given intravenously appeared in good concentration from both kidneys though the concentration from the left kidney was lower. The urea concentration from the right kidney was 0.5 per cent and that from the left was 0.4 per cent.

June 10, 1937: Excretory urography was performed and showed the right kidney pelvis and calyces to be slightly dilated. The left side was also slightly dilated but the degree of reduction of the hydronephrosis was considerable as compared with the preoperative roentgenograms. At this time she was readmitted to the hospital because of hypertensive cardiovascular disease. Her blood pressure was as high as 280 systolic and 140 diastolic. Splanchnic sympathectomy, celiac ganglionectomy and partial adrenalectomy on the right side were carried out. After a very stormy convalescence she left the hospital with improvement of her symptoms but with the blood pressure still markedly elevated.

FIG. 4. Intravenous pyelogram taken October 25, 1939, showing good function of left kidney with marked diminution in the hydronephrosis as compared with the pre-operative roentgenogram.

There were two further admissions to this hospital because of hypertensive cardiovascular disease. These were in December 9, 1938 and June 25, 1939. On her last admission her urine showed the following: Albumin, trace; specific gravity, 1026; microscopic, 1 to 2 red blood cells and a rare white blood cell. On October 6, 1939 the patient was admitted to Montefiore Hospital because of the marked hypertension. Intravenous pyelogram taken October 25, 1939 showed good function of the left kidney with marked diminution in the hydronephrosis (fig. 4).

SUMMARY

1. We presented a case of reimplantation of the ureter into the renal pelvis for trapped left kidney due to an aberrant renal vessel with marked stenosis of the ureter.

2. The postoperative valvular obstruction was relieved by cystoscopy and fulguration of the valve through the nephrostomy sinus. This is the first instance in the literature where such an obstruction was so treated.

3. The comparison of the preoperative roentgen-ray examinations with those taken as late as seven years after operation show a good functional result.

4. An accurate anastomosis between the ureter and pelvis is of paramount importance.

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THE SITE OF ACTION OF HYPNOTICS AND ANALEPTICS IN THE BRAIN*

ERNEST P. PICK, M.D.

This report is concerned mainly with certain investigations regarding the site of action of hypnotics and analeptics in the brain. It is, at the very outset, beset with some difficulty which lies in the fact that there is no exact method for the measurement of the intensity of the hypnotic effect and in the absence of a fixed point of reference, dependence must be placed on the comparative effects. Since the depth of narcosis is determined by the extinction of certain cerebral functions, the same device may be employed in judging the intensity of hypnosis. It must be admitted that such, more or less, arbitrary methods lack the desirable exactness of a quantitative physiologic experiment. Furthermore, sleep among different animal species varies in character and also in the ability to yield the different cerebral and spinal cord reflexes. One is, therefore, limited in the interpretation of the vestibular and the posture reflexes of Magnus (1) in the determination of the depth of narcosis and sleep. Hence, such methods can hardly be used in establishing the site of action of the hypnotics.

One can readily demonstrate in different bird species such as in the chicken and the pigeon how little is the influence of sleep, that specific alteration of consciousness, on the disturbance of the posture reflex. These birds will, even during sleep, preserve their equilibrium in a position which they maintain during consciousness and which to us may appear uncomfortable. Even during sleep, apparently, the posture reflexes of these birds are fully adequate (2). This is also true, within some latitude, even when sleep has been imposed by the application of hypnotics. Particularly noteworthy in this connection are the experiments of Fulton and his collaborators (3) who demonstrated the intact motor sensitivity of the cerebrum in the presence of profound anesthesia induced by derivatives of *barbituric acid*. Moreover, knee reflexes are found to be active even in the decerebrate animal under deep *Dial* narcosis. In fact, these reflexes are sometimes actually increased in dreaming humans or in sleeping dogs. Finally, we can refer to sleep-walkers who balance themselves on the edge of a roof and to the intoxicated piano player who, in spite of his alcohol narcosis, is capable of playing, without error, musical compositions familiar to him. This illustrates how difficult it is to judge the depth of sleep and

* Lecture given on February 7, 1940 at the Neuro-Pharmacological Seminar, Yale University, New Haven, Conn.

narcosis from the condition of the reflexes and to determine the site of action of narcotics.

The second great difficulty in determining the site of action of narcotics lies in the nature of these substances themselves. Depending on their physico-chemical properties and on the concentrations usually employed, they extend their effect to different parts of the brain and when administered in toxic doses they paralyze centers of the brain which are not concerned with induction of sleep. In this way paralysis of the vital centers, cardiac, respiratory and vascular, may occur as in deep alcohol narcosis or barbiturate intoxication. In order to exclude such wide effects of hypnotics, one must, in determining the site of action, study only their initial effects. In the later stages of sleep as in the more profound depths of narcosis one can no longer expect a limitation of the action to certain physiologically effective areas of the central nervous system because the most diverse portions of the brain are already under the influence of these lipoid soluble substances and the singling out of the specific area which is concerned in the actual induction of sleep is impossible.

In order to avoid these difficulties in answering the question as to which part of the brain is concerned in the induction of sleep by narcosis, the older experimenters extirpated certain portions of the brain. The experiences of Goltz (4), Rothmann (5), Karplus and Kreidl (6) with decorticated animals as well as the observation in newborn anencephalics (7) demonstrate that the transition from wakefulness to sleep may undoubtedly transpire in the absence of the cortex. It is not surprising, therefore, that Morita (8), following a suggestion by Hans Horst Meyer, was able to induce sleep with *chloral hydrate* and *urethane* in decorticated rabbits. In fact, the sensitivity to hypnotics of such decorticated and motor uninhibited animals is actually increased. The same is true also of the action of such derivatives of barbituric acid as *veronal*, *luminal*, *somnifen*, than of *chloretone* and *isopral*. Even if one removes the diencephalon with the preservation of the optic thalamus *alcohol*, *paraldehyde*, *urethane*, *magnesium chloride*, *veronal* and *luminal* can still produce sleep (Schoen (9), Yamawaki (10)). *Morphine*, moreover, a drug which is supposed to exert its main effect on certain portions of cortex, according to Amsler (11), Joël and Arndts (12) can produce sleep in decorticated animals. This, incidentally, is also true for scopolamine (Mehes (13) and Yamawaki (10)). With these experiments before us, it cannot be doubted that the cortex exerts a sleep inhibitory influence due to impulses which affect the deeper centers. A striking demonstration is offered by the well known centrally acting emetic, *apomorphine*, which, in the rabbit, produces excitement and fear reaction as well as an irresistible biting compulsion. When one decorticates such an animal the excitant will act as a hypnotic, like morphine (Amsler (14)). Also, *ergotamine*, which normally causes hyperexcitability and hyperthermia in rabbits (15) will produce in the thalamic

animal typical sleep (10, 13). With these experiments in mind scarcely anyone will deny that the cortex plays a role in the production of sleep. Rozansky (17) has shown how much the loss of the cerebral cortex changes the mechanism of sleep. If one decerebrates the monophasic sleeping pigeon or the polyphasic sleeping owl, the periodic sleep rhythm is interrupted; sleeplessness lasting for several weeks will ensue with only gradual return to the normal type of the sleep rhythm. Furthermore, it is precisely those hypnotics which belong to the *aliphatic* group, and are most closely related to *ether* and *chloroform*, such as *alcohol*, *chloral hydrate*, *chloralose*, *paraldehyde*, *amylene hydrate*, which affect at first the cerebrum (18). The suppression of sensibility before the abolition of motility and the initiation of true sleep—as it is practised in ether anesthesia induction—is also peculiar to *chloral*. Also, the release from cortical motor control by *paraldehyde* as well as the release of Sherrington's pseudo-pain center by *chloral* points to the primary suppression of the cortical and subcortical inhibitions (18, 20).

It is thus of little value to employ these exclusion experiments in the localization of the hypnotic effects. Attempts, therefore, were made to determine whether or not, in the intact animal, the reactive influence of the vegetative centers (which, it is believed, are situated in the subthalamic region of the brain stem) or the effect of certain well localized disease of the brain stem (such as chorea, paralysis agitans or post-encephalitic Parkinsonism) will offer a clue as to the site of action of hypnotics. In this connection it is known that the motor nuclei of the brain stem which are involved in chorea are extremely well influenced by barbiturates such as *Veronal*, *Phenobarbital*, and *Nirvanol* and also by the *trichlorisobutyl alcohol* (*Chloretone*). It is also known that here is their primary site of action. The excellent effect of the *solanaceen alkaloids* such as *scopolamine* and *hyosciamine* upon post-encephalitic Parkinsonism substantiates the localization of the initial effect within the brain stem as also does the production of twilight sleep with *scopolamine* and *morphine* (18, 20). Furthermore, the effect of *Bulbocapnine* in Parkinsonism and the production of Bulbocapnine catalepsia makes certain the localization of the site of action in the brain stem (19).

The suppression of emetic effects before the production of sleep brought on by *barbituric acid* derivatives as well as by *Chloretone* or some *Valerian* preparations seems also to be evidence favoring the observation that the first site of action of these substances lies in the emetic center situated in the brain stem (15, 22). No less significant is the fact that the decreased irritability of the vegetative centers of the brain stem caused by some hypnotics occurs prior to the production of sleep. It possibly represents a useful localization principle. Among these are the inhibition of water metabolism by certain hypnotics, especially barbituric acid derivatives (21),. the lowering by *Luminal* of the increased metabolism induced by

thyroxin (23), central antipyretic effects (27), the reduction by *barbiturates* of those secretions dependent on stimulation from the central nervous system (24), the secretion of bile (25), and the production of hypoglycemic adrenalemia in contrast to the effects of hypnotics of the *aliphatic* series such as chloral, paraldehyde, and others (26). This selective localization becomes evident also in certain reflex processes of the vegetative nervous system. For example, the vagus cardiac reflex is inhibited by certain hypnotics (28) such as the barbituric acid derivative, *Pernocton*, in contrast to the ineffectual *chloralose* which acts upon the cortex only. Similarly, *Pernocton* has a severe action on the carotid sinus reflex while *chloralose*, even during deepest sleep, does not influence this reflex at all (29). Even direct injection of different hypnotics into the cisterna magna discloses striking disparity of the effects between the two groups of hypnotics, namely, the *chloral* or cortical hypnotics on the one hand and the *barbiturates* or subcortical, thalamic hypnotics, on the other (30). Also a great number of motor and sympathetic reactions which are associated with the emotions of rage and fear (mydriasis, erection of the hair, extrusion of the claws, clawing and fighting movements, etc.) are diminished or abolished after intravenous or intraperitoneal injection of *sodium amytal*, a barbituric acid derivative. Moreover, these sympathetic reactions to stimulation of the hypothalamus can be elicited even with the animal under light ether anesthesia (I. H. Masserman (31)). Furthermore, one may refer to the histologic changes in the brain stem, thalamus and hypothalamus which numerous authors have found after the administration of barbituric acid derivatives while the cerebral cortex itself revealed no degenerative changes. I refer to such changes observed following administration of *Somnifen* (van der Horst (32)), of *Luminal* (Sahlgren (33)), and of *Medinal* (Hoff and Kauders (34)) and of other barbiturates (35). One must mention here the bulbar symptoms (slurred speech, ataxia, bradycardia, disturbances in swallowing, suppression of cough and vomiting reflex) which were observed following Somnifen sleep therapy introduced by Klaesi (36). The experiments performed by Demole (37) in which cats were injected with the smallest amounts of *calcium chloride*, into the grey parainfundibular areas with the production of sleep lasting for several hours and similarly the production of sleep by the injection of *Ergotamine* into the lateral or third ventricles (Hess (38)) are of significance.

All of these experiences point to the fact that there are two groups of hypnotics. There is *first*, that group which affects primarily the subcortical brain stem nuclei, particularly those of the thalamic and subthalamic regions. From these, the state of sleep is apparently induced. The main members of this group are the barbituric acid derivatives such as *Chloretone*, *Nirvanol*, *morphine*, *scopolamine*, *Ergotoxine*, and others. The *second* group of hypnotics, comprised mainly of the aliphatic series, such as *alcohol*, *chloral hydrate*, *chloralose*, *paraldehyde*, *amylene hydrate*, *avertin* and

bromides exert their effect primarily upon the sensory cortex and secondarily radiate to the motor cortex. The hypnotics of the first group may be called *brain stem* or *subcortical* or *thalamic hypnotics*, while those of the second group have been called *cortical hypnotics*.

It is not without importance, that the electro-encephalogram presents marked differences in the two groups as shown by the investigations of Berger (39), Bremer (40), van der Horst (41), and Kornmueller (42). However, I should not like to enter into a discussion of the interpretation of these electro-encephalograms since they are still in the process of elucidation.

The previously mentioned difficulties, particularly the lack of an exact method of determining the effectiveness and site of action of narcotics make the facts just detailed highly probable but not absolutely certain. Even the findings of the Keesers (43) are not a strict proof for the localization of the action to the brain stem. They administered small doses of heavy metal salts of the barbituric acid and were able to demonstrate them in the brain stem exclusively.

Therefore, a more exact method for ascertaining the point of action of hypnotics had to be found. From the investigations of Winterstein, Warburg, Holmes (44), and others, it is known that the brain, particularly its gray substance, has a very active oxidative metabolism during which heat is engendered. This metabolic activity is inhibited by anesthetics, narcotics, and hypnotics. The same effects are noted in experiments on surving portions of brain as performed by Quastel (45), Gerard (46) and collaborators. Crile and Rowland observed depression of the brain temperature during ether anesthesia (47).

In order to obtain exact measurements which would be independent of any change due to perfusion and blood temperature a new method was required. Such a method has been devised by my co-worker, Dr. Feitelberg, in collaboration with Lampl. They introduced delicate thermocouples into the cortex, the brain stem and into the internal carotid artery and measured the temperature differences continuously by means of a potentiometer method. Since, at the same time the readings are recorded on a kymograph, a precise record of the temperature changes can be obtained in the form of a curve. Such records can also be obtained in unnarcotized animals by previously, under sterile conditions, implanting the thermocouples into the brain and carotid artery and allowing them to heal in at the sites of implantation. This method is very sensitive and will even permit the recording of minute variations in heat productions providing they exceed $\frac{1}{200}$°C. It was demonstrated that heat production, under the influence of various narcotics and hypnotics, will be depressed in the cerebral cortex as well as in the brain stem. The brain temperature which normally exceeds that of the blood, can be depressed to the level of the blood temperature and even below that. This lowering may amount to

as much as 0.2° to 0.5°C. and more. This is an exact readily measurable, objective criterion for the evaluation of the effects of narcotics, borne out by experiments with *ether*, *paraldehyde*, and *luminal*. If one studies simultaneously the effect upon different portions of the brain, one can record the significant observation that not all areas of the brain are equally affected by narcotics. By differential measurements one can demonstrate that *ether* as well as *paraldehyde* will cool the cortex more than the brain stem, while conversely, *phenobarbital* will cool the brain stem more than the cortex. It can thus be proven with certainty that *ether* and *paraldehyde* in the employed concentrations will influence primarily and most intensely the cortical gray substance while *luminal* will affect predominantly those oxidation processes localized in the brain stem and to a lesser degree, the cerebral cortex. It is clear that the longer duration and the increased depth of sleep effects will lead to a gradual reduction of metabolism to the same level in different portions of the brain. This follows because the inhibition of one area in the brain will release inhibitions in other areas. Ether as well as paraldehyde will secondarily affect the brain stem after a few minutes. Conversely, the luminal effect will be extended to the cortex either directly or indirectly through interruption of the thalamo-cortical impulses. The inhibition of the oxidative processes in the gray substance may also lead to a reversible exclusion of various nervous functions whether they be in ganglia or in the conductive apparatus. Thereby, distantly located suppression and interruption of nervous impulses may take place. So much for the investigations which have thus far been carried out (48).

Investigations concerning the analeptics and their site of action in the brain were carried out first with the most modern drug, *Cardiazol* (Metrazol) and its relationship to various hypnotics was studied. It can be stated that *Cardiazol* exerts an awakening effect against drugs of the *chloral hydrate* group as well as against the *barbituric acid* derivatives although the various antagonisms are not equal. This is best illustrated by an example of converse action in which *Cardiazol* convulsions are most readily and rapidly arrested by *barbituric acid* derivatives and not by *chloral hydrate*, *avertin* and *paraldehyde*. The most accurate information concerning the site of action is available through heat production observations. It was found that *Cardiazol* will affect the cerebral cortex as well as the brain stem by stirring up the oxidative processes in both places to a remarkable degree. The temperature rises almost 0.5°C. However, if one records a *differential thermogram* by simultaneously measuring the difference in temperature increase of cortex and brain stem one finds that the effect is exerted primarily and predominantly on the brain stem and will only later gradually extend to the cortex. It can be readily understood therefore that *Cardiazol* is an antagonist for brain stem as well as cortical hypnotics although its main action appears to be applied to the brain stem (48). These state-

ments are in complete agreement with the most recent investigations of Masserman (49) who found that *Metrazol*, when applied directly to this region of the diencephalon, stimulates the vegetative and emotional mimetic functions of the hypothalamus. Incidentally, it seems that similar effects can apparently be attributed to *Picrotoxin*, a conclusion in accord with other findings, namely, that the effects of *Picrotoxin* on the hypothalamus are similar in many respects to those produced by *Metrazol* (Masserman and Rodholm (50)). The effects of *Picrotoxin* upon the spinal and medullary centers have been known for a long time and make it probable that *Picrotoxin* convulsions are produced rather by stimulation of the brain stem than of the cerebral cortex. In contrast to this, we know that camphor and cocaine convulsions originate in the motor centers of the cortex because they are no longer seen in decerebrate animals while *caffeine*, *Metrazol*, and *Hexeton*, according to Schoen (51), are still effective in such animals. Caffeine, however, seems to be one of the weakest analeptics since it does not exert an antagonistic effect in profound intoxications by hypnotics, nor does it vitiate narcolepsy or even deep alcohol intoxication. Among the remaining centrally stimulating agents I should like finally to mention briefly two of them, *Ephedrine* and *Benzedrine*. Both are phenyl bases with a good peripheral sympathico-mimetic action upon blood vessels and smooth muscle. In addition, they have an excellent central effect which even allows the use of both as a good antagonist in narcolepsy. If one investigates these two analeptics by means of the differential determination of the temperature changes in the carotid artery and grey substance of cortex and brain stem in cats, one finds after the subcutaneous injection of only 0.01 Gm. an increase in heat production in these cerebral areas which may amount to over 0.5°C. (52). This increase in heat production may persist for several hours. One can, therefore, readily understand that these substances, which so strikingly stir up the energy processes of the brain also serve as effective agents of central stimulation. According to the older investigations of Gaddum (53) and the more recent work of Quastel (54) these two substances appear to hinder the production of amino-acids by means of the suppression of amino-oxidases, thus inhibiting the oxidative processes in the brain. This may serve as another mode of increasing the oxidative metabolism of the brain by these two phenylamine bases. Investigations concerning the point of action in the brain of these two substances have not yet been initiated. This problem must be added to the many not yet solved, about which I can only hint at the present time.

The foregoing remarks invite a brief reference to the various pathological and clinical observations bearing on the subject of a center regulating the sleep-waking rhythm. These observations add to our understanding of the site of action of hypnotics. The investigations of Economo (56) on encephalitis lethargica have established quite definitely the location of a

sleep regulating center, hitherto postulated by the Viennese ophthalmologist, Mauthner (55) as located somewhere in the gray matter enveloping the third ventricle and the Sylvian aqueduct. Economo was also the first to mention the important influence of the vegetative centers in the hypothalamus on the action of the sleep regulating center. Several later investigations of other lesions in the neighborhood of the third ventricle and of the posterior portion of the hypothalamus show similar sleeping disturbances described by Economo in cases of encephalitis lethargica. Here it is necessary only to mention the observations made partly on suppurative lesions, partly on tumors situated in the same region of the brain-stem (Luksch (57), Adler (58), Fulton (59), Globus (60)). Besides changes in the sleep-waking mechanism, similar lesions also produce sometimes other vegetative disturbances, for instance, in water-balance, heat regulation, vasomotor mechanism and other vegetative dysfunctions (Globus (60)). Finally among the important experiments carried out to determine the hypo- or sub-thalamic sleep regulating center may be mentioned the work of Mehes (61), Spiegel and Inaba (62), Hess (63), Demole (64), Ranson (65) and recently of Miller and Spiegel (66). All these investigations seem to show that mechanical, electrical or chemical alterations in the mentioned hypothalamic area produce somnolence or sleep lasting several hours or even days. The mechanism, however, which produces the state of normal drowsiness or the state of abnormal sleep following the damage of the hypothalamic area or the sleep imposed by hypnotics is still under investigation. The study of this problem seems to offer good opportunities and is important enough to call for new experiments in this field.

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TUBERCULOSIS OF THE CHEST WALL: HEALING AFTER OPERATION FOLLOWED BY RADIOTHERAPY (FIVE AND ONE-HALF YEAR RESULT)

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The literature contains numerous reports on the *immediate* results of various types of treatment for tuberculosis of the chest wall. The following case is of interest because a good result has been confirmed by frequent observation over a period of five and one-half years.

CASE REPORT

History (Adm. 413565). J. B., aged ten and a half years, was admitted to the hospital on October 29, 1935. Six months earlier the child had been admitted to another hospital because of an acute left pleural effusion. He remained there for two and a half months. The effusion was not aspirated, but was considered to be of tuberculous origin on the basis of a strongly positive Mantoux reaction. No evidence of pulmonary tuberculosis or of tuberculous disease elsewhere was found.

After leaving the hospital the patient was well except for slight loss of weight. Two weeks before admission, he complained of pain in the left lower axilla and his mother noted the appearance of a slowly enlarging mass in this region. For five days there had been slight fever but no dyspnea, cough, or other manifestation referable to the chest.

The developmental and past history were negative. The mother, father, and five siblings were alive and well, with no evidence of familial tuberculosis.

Examination. The patient was a well developed, well nourished boy who was not acutely ill. The cervical and inguinal lymph nodes were palpable. A soft bulging, warm, tender mass was noted in the left axilla, extending from the sixth to the twelfth ribs. Flatness on percussion and distant breath sounds were heard in this area, but no abnormal physical signs were noted elsewhere in the chest. Cardiac dullness was normal in extent, and the heart sounds were of good quality. A short systolic murmur which was not transmitted was heard in the mitral area. The remainder of the examination was negative. The temperature was 99.6° F. in the morning, rising to 101° F. at night. The pulse rate ranged between 98 and 120 per minute. The respiratory rate was 20 to 22 per minute.

Laboratory Data. Urine, negative. Blood: hemoglobin, 68 per cent (Sahli); red blood cells, 4,800,000; white blood cells, 10,000 with 76 per cent polymorphonuclear leucocytes and 24 per cent lymphocytes.

An x-ray examination of the chest was reported as showing the soft tissue mass to be mainly at the level of the ninth rib in the left axilla. The roentgenogram showed a periostitis of the tenth rib suggesting involvement by an inflammatory process. A small semicircular shadow was present just above the level of the left leaf of the diaphragm, adjacent to the spine. Its nature could not be determined from the x-ray examination; the spine in this region showed no abnormality.

Course. The diagnosis of *empyema necessitatis* was suggested, but the x-ray

examination failed to show a shadow indicative of empyema. A "cold" abscess of the chest wall was considered, especially in view of the markedly positive Mantoux test, but the local findings of heat and tenderness suggested that if it were one, secondary infection had occurred. On the basis of the x-ray appearance of the tenth rib showing periosteal proliferation and other evidences of osteomyelitis, the diagnosis of osteomyelitis with extrapleural abscess was also considered.

It was suggested that the mass be aspirated and if the pus showed no bacteria or only acid fast bacilli, to assume that the abscess was tuberculous and to treat the lesion by repeated aspiration. If pyogenic organisms were found, incision and drainage was to be performed.

Aspiration yielded thick pus, smear of which showed gram positive cocci in short chains. (Acid fast bacilli were found on later examination.)

Operation. Under general anesthesia an incision was made parallel to and over the tenth rib. The area of swelling was incised and about two drams of brownish pus and some pultaceous brownish material evacuated. A small, smooth, well-defined fistulous tract was found, extending deeply between the ninth and tenth ribs, into which a probe could be passed; the tract was found to extend under the ninth rib. Small portions of the ninth and tenth ribs were excised with their periosteum, and their under surfaces were seen to be slightly irregular, but smooth. A pocket about two inches in diameter was exposed and contained a small amount of fairly dense yellowish material which could be removed from the underlying layer of whitish tissue (apparently the endothoracic fascia). In the process of removing this yellowish material with a curette, the parietal pleura, which was thin and apparently uninvolved was exposed. The intercostal tissues were thickened and infiltrated, and were excised. The entire cavity was packed lightly with iodoform gauze.

The specimens of the ribs and extrapleural tissues were reported as showing tuberculous involvement. The gram positive cocci seen on smear of the pus did not grow either aerobically or anerobically.

Postoperative Course. Excessive granulation tissue appeared in the wound. A specimen sent for examination four weeks after operation was reported as tuberculous granulation tissue. On December 4, 1935, five weeks after operation the patient was discharged to the Out-Patient Department for further treatment of the wound. There was a persistent sinus which discharged purulent material. However, the child appeared well and had gained in weight.

An x-ray examination of the chest on March 17, 1936 revealed a shadow suggestive of a similar extrapleural exudate in the left axilla at the level of the fourth rib; evidences were also seen of enlarged tracheo-bronchial nodes. The circular shadow adjacent to the eleventh and twelfth vertebra was still present, but special examination of the spine revealed no evidence of Pott's disease. X-ray therapy of the wound was decided upon and between May 5, 1936 and July 1, 1936, the patient received 1200 "r" units to an 8 x 3 cm. field. When seen on October 22, 1936, the sinus had healed completely and the child was well.

The patient has been seen in the Follow-Up Clinic on frequent occasions, the latest being January 20, 1941. He has remained completely well. Repeated x-ray examinations of the chest have shown no abnormalities in the lungs.

DISCUSSION

Tuberculous involvement of the chest wall is frequently secondary to needle-track infections after aspiration of an empyema, or following surgical procedures for pulmonary tuberculosis. Rarely, it may be due to infection burrowing along the intercostal structures from an osteomyelitis

of the spine. Tuberculous abscess unassociated with such processes is a relatively uncommon condition. It is apparently much more frequent in European countries where it is associated by some authors with the higher incidence of infection with bovine type bacilli and, thus, greater incidence of tuberculous adenitis. Barrett (1) points to the fact that such tuberculous abscesses are most common in the region, anteriorly, of the costo-chondral junctions and, posteriorly, of the junction between the transverse processes and the ribs. These sites correspond with the location of the two main groups of lymph nodes of the chest wall in the plane of the endothoracic fascia. Involvement of these nodes by the hematogenous route would account for the incidence in these regions.

Experimental evidence has been shown of rapid development of lymphatics in newly formed pleural adhesions. In addition, it has often been noted that small lymph nodes found in the intercostal tissues during thoracoplasty are tuberculous. The passage of tubercle bacilli through these pleural lymphatics from a tuberculous lung or from a pleural effusion has been considered by many to be a mode of origin of these chest wall abscesses. However, Barrett reports that during operations on several cases he has accidentally opened the pleura and has found it to be normal with no adhesions present. In many cases, no evidence of underlying lung disease, or of previous pleural effusion can be found. These facts point to the possibility that at least some of these abscesses may be due to hematogenous infection of the intercostal lymph nodes.

Some writers have stressed the origin of these abscesses from tuberculous osteomyelitis and osteochondritis, but others have pointed out that the infection usually arises in the periosteum or in the perichondrium rather than in the substance of the rib or cartilage.

In the case reported, it would seem that the intercostal lymph nodes were involved primarily by the hematogenous route, inasmuch as the pleura seen at operation was apparently normal. The smooth appearance of the ribs on their inner surfaces, with superficial location of the diseased portion, point to their involvement by contiguity. Secondary infection such as occurred in this child is not uncommon.

The surgical treatment of this condition yields good results when every bit of infected material is removable. Dr. A. V. Moschcowitz wrote extensively on this subject and pointed out that in involvement of the anterior fused cartilages, the disease would spread from one to the next if removal of infected tissues was incomplete. In cases such as the one reported, in which the inner wall cannot be removed, the results from surgical treatment alone are not satisfactory. The excellent result in the reported case is apparently referable to radiotherapy.

Those who prefer non-surgical treatment point to the well-known belief that tuberculous wounds will not heal, and prefer to treat cold abscesses by repeated aspiration of the fluid contents and replacement by liquefying

and antiseptic solutions such as Gauvain's solution. However, even when the aspiration is done by inserting the needle through healthy tissue, sinuses are frequent complications, and good results are few. When secondary infection supervenes, as in this case, surgery is unavoidable.

Much has been written on the beneficial effects of heliotherapy, and to a lesser extent on radiotherapy in lymph node and bone tuberculosis. There are great differences of opinion between those who have advocated such treatment as an adjunct to surgery and those who have felt that surgery was unnecessary except in very unusual cases. However, there is scarcely any literature which deals specifically with tuberculosis of the chest wall since such cases seem to have been included in the above groups.

Iselin (2) reported the only series of cases of tuberculosis of the chest wall which were treated by radiotherapy without surgery. Forty of his fifty-seven cases treated from 1909 to 1915 were healed; seven did well but did not heal because the patients died from pulmonary or osseous tuberculosis. From 1915 to 1917, twenty cases were treated; sixteen of these cases were cured, two were unimproved and two patients died with their thoracic wall lesions unhealed. The 72.7 per cent of cured cases seems surprisingly high, especially since no necrotic bone or cartilage was removed surgically. As yet there has been no confirmation of such success by radiotherapy from other observers.

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VITAMIN B_1 EXCRETION STUDIES IN A CASE OF ALCOHOLISM WITH NEUROPATHY

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[*From the Medical Services*]

Since the relationship of peripheral neuropathy to vitamin deficiency was first suggested by Wechsler (1) ten years ago, the elucidation of the problem has been considerably advanced. The isolation and synthesis of thiamin, the first of the vitamin B complex to be so obtained, was followed by further development of a vast literature concerning its therapeutic use. Most investigators, however, have depended upon gross clinical changes to establish the diagnosis, or to evaluate the efficacy and dosage in treatment of vitamin B_1 deficiency. Using a relatively simple method for the determination of vitamin B_1 active substances in the urine developed by Schultz, Atkins and Fry, (2) we have been able to obtain data concerning these problems (3 and 4).

This paper is concerned with urinary excretion studies on a patient with chronic alcoholism, peripheral neuropathy, and pulmonary tuberculosis, who received large doses of vitamin B_1 parenterally.

CASE REPORT

History (Adm. 451738). A 38 year old Irish-American hearse-driver, was admitted to the hospital on January 27, 1940. He complained of dyspnea, ankle edema, and weakness of the lower extremities with lancinating pains in the legs, of about two weeks duration. In addition he had noted a cough for a period of three days. He had been accustomed to drinking at least a half pint or more of whiskey daily for many years. One year prior to admission to the hospital he claimed that he had been ill with similar symptoms which subsided after a two week period of bed rest. Because of mental clouding his history could not be ascertained in greater detail. His wife supplied information regarding his diet and it was notably lacking in fresh fruits, vegetables, milk, eggs and meat.

Examination. The patient was a well developed but poorly nourished male, who was slightly dyspneic and whose voice was hoarse. There were signs of diffuse bilateral pulmonary tuberculosis. The heart was enlarged, with a diastolic gallop rhythm present at the apex, short apical and basal systolic murmurs, and a rate of 110 per minute. The blood pressure was 180 systolic and 80 diastolic. The liver was enlarged 2 finger-breadths below the costal margin. There was no evidence of ascites or splenic enlargement. There were no skin or mouth lesions other than some exudate on one tonsil. Neurological examination revealed the absence of all deep and superficial reflexes, absent plantar responses, marked muscle weakness of the thighs, legs, and arms, marked tenderness of the calf and hamstring muscles, and diminished sensation for all superficial modalities in the toes and fingers. The psyche was clouded and hallucinations were present.

Laboratory Data. Sputum examinations were negative for acid-fast bacilli, but a biopsy specimen of the tonsillar lesion proved to be positive. X-ray examination of the chest revealed diffuse tuberculous infiltrations throughout both upper lobes. An electrocardiogram revealed depressed RT 2 and 3, diphasic T 4; subsequently T 4 became upright and RT 4 depressed. The circulation time and venous pressure were normal. The blood Wassermann reaction was negative. The Takata Ara test was 3 plus, and the icterus index was 6; the urine examination was negative. The white blood count was 20,600; of which the polymorphonuclear leucocytes were 86; lymphocytes, 9; monocytes, 5 per cent. Plasma ascorbic acid was 0.534 mg. per cent. His response to the 1 mg. "load test" of thiamin was 85 gammas of thiamin activity recovered from the urine in four hours, an extremely low figure.

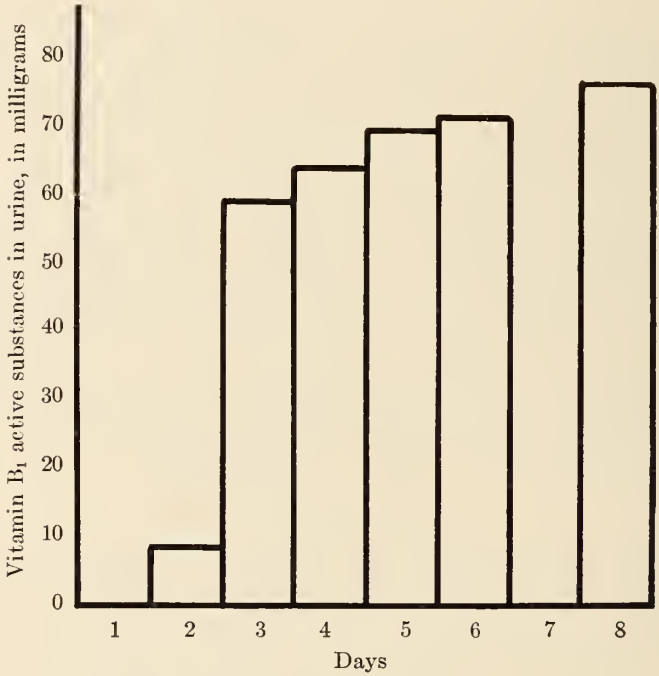

Chart showing the urinary excretion of vitamin B_1 active substances following daily intravenous administration of 100 mg. of vitamin B_1.

Course. The patient became progressively worse with respect to his tuberculous lesions which were of the fulminating type. His temperature ranged between 101° to 104°F. intermittently. Because of the flagrant tuberculous character of the disease, it became impossible to keep the patient in a general hospital and, therefore, after ten days, he was transferred to an institution for tuberculosis, where he died soon after.

DISCUSSION

Vitamin B_1 Studies. When the 1 mg. "load test" corroborated the clinical picture of vitamin B_1 deficiency, the patient was given 150 mg. of nicotinic acid and 100 mg. of thiamin hydrochloride, intravenously, daily. The total urine output for each 24 hour period was collected and

assayed, that of the first and seventh days being discarded because the collection was incomplete. The graph indicates the amazingly low excretion of but seven milligrams of vitamin B_1 active substance after the *second* injection of 100 mg. of thiamin. This is the lowest response we have observed so far, and may be interpreted as indicating retention of almost all the vitamin B_1 administered during the first two days. On succeeding days there was a progressive stepladder rise in excretion, so that by the ninth day 80 per cent was recovered following the injection of 100 mg. of thiamin. Even in as severe a deficiency as this patient presents, it is evident that treatment with large doses for one week is adequate to establish a fair degree of saturation and, thereafter, the dosage may be reduced. Unfortunately, this individual could not be studied further in this hospital because of his active tuberculosis.

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LOCALIZED TUBERCULOUS PLEURAL EFFUSION SIMULATING PULMONARY NEOPLASM

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Although the onset of pulmonary tuberculosis may frequently present a bizarre clinical syndrome, the x-ray picture is ordinarily not difficult to interpret. When such a difficulty does arise it is usually due to the confusion of a tuberculous lesion with other inflammatory diseases.

If the tuberculous process is first manifested by a pleural effusion, the underlying pulmonary lesion may be obscured. Aspiration of the fluid may lead to the diagnosis either by the finding of the tubercle bacillus, or by permitting the hidden lesion to be visualized radiographically. For the effusion itself to cast a shadow which simulates a pulmonary neoplasm is an unusual occurrence. Such a misinterpretation of the x-ray film occurred in the case which is presented. An exploratory thoracotomy revealed this error but, nevertheless, was not successful in disclosing the correct diagnosis.

CASE REPORT

History (Adm. 424196) E. A., a white male engineer, 43 years old, was admitted to The Mount Sinai Hospital on February 15, 1938. He had had a chronic cough for six to seven years, with the production of a small amount of whitish sputum in the morning. This cough had been intermittent up to eighteen months prior to admission, but since that time had become persistent and the expectoration was frequently blood-tinged. Eight weeks before admission the cough became worse and one night he was suddenly awakened from sleep by pain in the left anterior chest. The next morning his temperature was 103°F. He remained in bed and after three or four days all the symptoms subsided, he returned to work. He felt weak and occasionally was short of breath but, nevertheless, gradually improved. Two weeks before admission his symptoms again became more severe. The cough increased and his temperature rose to 102° F. Six days before admission his physician aspirated fluid from his left chest. His family history and past history were irrelevant except for the occurrence of uncomplicated pneumonia at the ages of twelve and twenty-seven years.

Examination. The patient was a well developed, obese, white man. The only significant findings were flatness anteriorly and posteriorly as well as in the axilla of the left chest. Breath sounds and fremitus were absent over the lower left chest and bronchitic wheezes could be heard over the entire thorax.

Laboratory Data. The blood pressure was 117 systolic and 70 diastolic. Hemoglobin, 90 per cent; red blood cells, 4,900,000; white blood cells, 5,100 with 61 per cent polymorphonuclear neutrophiles. The sputum was negative for tubercle bacilli; urine, negative; blood urea nitrogen, 9 mg. per cent; blood sugar, 85 mg. per cent. The blood Wassermann reaction was negative.

X-ray examination of the chest on February 16, 1938 revealed a round, sharply demarcated shadow in the posterior portion of the left lower lobe above the costophrenic sinus, extending from the level of the ninth to the eleventh ribs. This shadow had the appearance of a neoplasm. There was a small collection of air and fluid beneath this shadow, and the pleura was markedly thickened (Fig. 1).

Bronchoscopy on February 21, 1938, showed a small amount of non-odorous secretion from the apical division of the left lower lobe. There was no evidence of neoplasm.

Lipiodol bronchogram on February 23, 1938, showed the branches of the left bronchus to be fairly well outlined with no definite abnormality. The branches of the left lower lobe in the vicinity of the pulmonary shadow were poorly shown. On February 25, an x-ray examination of the ribs showed no abnormality. The left

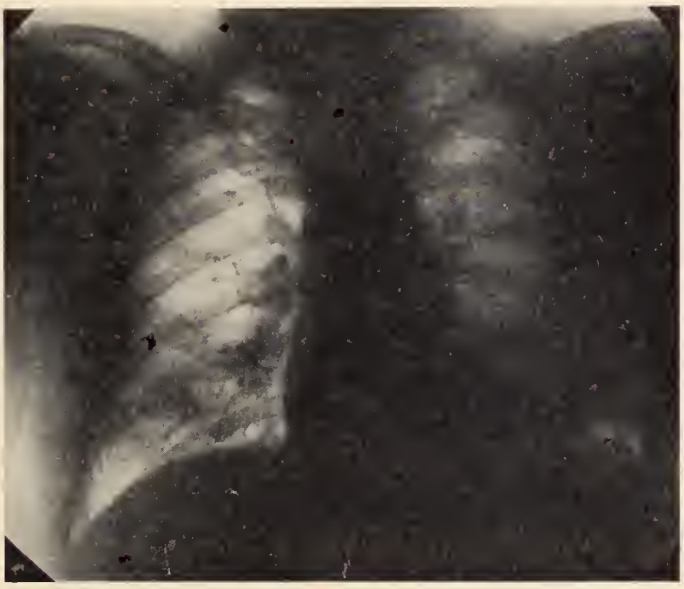

FIG. 1

chest was aspirated and 13 cc. of straw-colored fluid were removed. The specific gravity was 1019; total cell count, 5,020; white blood cells, 4,220 with 92 per cent small lymphocytes. No organisms were seen on smear. Culture and guinea pig inoculation were negative.

Operation. Although no definite diagnosis could be made, it was felt that surgical intervention was indicated. An exploratory thoracotomy was performed on March 1, 1938 by Dr. Harold Neuhof. Avertin and nitrous oxide and oxygen were used for anesthesia. Through a posterior lateral approach, a liberal portion of the eighth rib was excised. The pleural cavity contained a small amount of slightly cloudy fluid. The visceral pleura over the lower lobe was chronically inflamed and appeared as a parchment-like membrane. No mass could be felt within the lung. There were numerous small collections of fluid within the pleural cavity adjacent to the large effusion. There was no evidence of tuberculosis. It was evident that the shadow seen on x-ray examination was an encapsulated collection of fluid between the undersurface of the lower lobe and the diaphragm. The pleural cavity was packed lightly

with gauze. A specimen was removed and pathological examination revealed "fibrin with purulent exudate."

Postoperative Course. Following the operation the temperature ranged between 100° and 104°F. On numerous occasions there was retention of pus in the pleural cavity. This was controlled by irrigations. X-ray examination on March 18, showed small mottled infiltrations throughout the entire left lower lobe, which were thought to represent areas of bronchopneumonia. Another x-ray examination on April 7, showed a considerable degree of resolution of the process in the left lung. There were also a few faint infiltrations in the right lower lobe, which had been noted on previous films. As an aid to obliteration of the pleural space, a left phrenic exeresis was performed on April 1. The patient was still running a low grade fever and the wound was showing very little tendency to heal, when he asked to be discharged on April 13, 1938.

He was seen in the Follow-Up Clinic on May 17, 1938, at which time his wound had still shown no sign of repair, the fever had continued, and his general condition was slowly deteriorating. He was readmitted to the hospital on that day for a transfusion and further work-up. The hemoglobin at that time was 66 per cent.

X-ray examination, performed on May 19, was reported as follows: "Since the last examination, there has occurred an extension of the processes previously reported in the left lower lobe. Now in addition to interstitial infiltrations previously reported throughout this lung, there are mottled shadows of consolidation denoting a more intense exudative process beneath the left clavicle. In the mesial portion of this, there is an area of increased aeration which may represent a cavity. Throughout the right lung there are innumerable submiliary nodules and in the mesial portion at the apex of the lung there is an area of irregular consolidation. There still remains a small area of pneumothorax over the left lower lobe."

The appearance was now suggestive of a tuberculous process with submiliary spread throughout the entire right lung. The patient was, therefore, transferred on May 21, 1938, to a sanatorium for treatment of his tuberculosis.

COMMENT

A pleural effusion in this case closely simulated the x-ray picture of a pulmonary neoplasm. In the absence of any other positive findings either confirming or denying the diagnosis of neoplasm, an exploratory thoracotomy was performed. This procedure eliminated the possibility of the lesion being neoplastic, but nevertheless did not aid in making the correct diagnosis. The correct diagnosis was determined only when the disease had progressed sufficiently to present a typical clinical picture of pulmonary tuberculosis.

THE ELECTROCARDIOGRAPHIC CHANGES AFTER EXERCISE IN ANGINA PECTORIS[1]

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Angina pectoris due to coronary artery disease is usually characterized by substernal pain associated with exertion. Even when such a history is present, however, objective evidence of heart disease, as indicated by changes in the electrocardiogram, cardiac size and pulsations, exercise tolerance and vital capacity, may be lacking. Usually, at least one of these tests is abnormal; rarely they are all normal. It is particularly in such a case that any additional means of confirming the presence of coronary artery disease is valuable. Such a method is provided by changes in the electrocardiogram produced by exercise (1–6). These consist of depression of the RS-T segment and lowering or inversion of the T-wave in one or more leads. In the presence of disease of the coronary arteries, effort results in insufficiency of the coronary flow, since the work of the heart is increased without compensatory increase in blood flow in the narrowed arteries. Alterations in the electrocardiogram and precordial pain may follow. Similar changes may be observed in spontaneous attacks of angina pectoris (1, 2, 7) and whenever coronary insufficiency is present, regardless of the etiological factors, such as aortic stenosis, shock, operation, acute hemorrhage, tachycardia (8).

Anoxemia of the heart muscle, associated with pain and changes in the electrocardiogram, has been induced by a number of investigators as part of a generalized anoxemia, following rebreathing (9, 10). When exercise has been used in the past, it has been the custom to continue the exertion until the patient complained of pain. However, it seemed to us essential to standardize the amount of work performed, in order to have a basis for comparison in different subjects. For this purpose the two-step exercise tolerance test of Master (11) is applicable, since it is based upon the optimum work for each person. When normal subjects perform the test there are no significant changes in the electrocardiogram (12); only after excessive exertion may slight changes occur normally (5). In patients with organic heart disease depression of the RS-T segment over 1 mm. and lowering or inversion of the T-waves occur in half the cases (12). Consequently a negative result does not exclude the presence of coronary sclerosis; however, the latter is indicated by a positive result.

[1] Presented at Grand Rounds, First Medical Service February 23, 1940.

The test is simple to perform. A control electrocardiogram is taken first. With the electrodes still attached, the patient climbs the designated number of steps as determined by his sex, age and weight. The electrode wires are immediately connected and an electrocardiogram taken as rapidly as possible, preferably within one minute. Another control record is made five minutes later. The test may be carried out by one person, although a little time may be saved by having an assistant connect the wires immediately after the exercise. At the same time, the assistant can also record the heart rate and blood pressure before and after exercise, to determine the exercise tolerance of the patient.

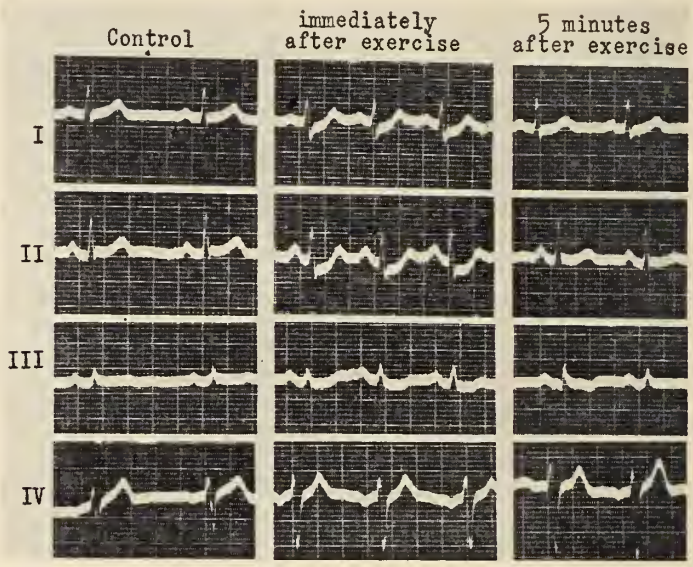

FIG. 1. The control record is normal. The record taken immediately after exercise shows depression of the RS-T segment in the three standard leads; T-3 is diphasic. Five minutes later, only slight depression remains in lead I and T-3 is inverted.

CASE REPORT

History. (Adm. 450742) The patient, a man fifty-eight years of age, entered the hospital for the first time nine years ago with symptoms of duodenal ulcer. When a medical regime did not afford relief, a partial gastrectomy was performed. He felt well for six years, and then complained of pain in the right loin. One year later a laparotomy was performed at another hospital, and the right kidney was found to be ptosed and mobile. At this time there were no cardiac symptoms or signs. The blood pressure was 105 systolic and 65 diastolic. One year and a half ago the patient began to experience pressure over the precordium when he walked, which was relieved by rest. As time went on he suffered attacks of pain beginning in the upper part of the back, and radiating into the arms and underneath the sternum. Recently these attacks became more severe and occurred frequently at rest and even in sleep. There was questionable relief with nitroglycerine.

Examination. The patient was of asthenic habitus and hypersensitive to the Libman test. The fundal vessels were normal. The lungs were clear. The heart sounds were of good quality and regular. There were no murmurs. The liver was not enlarged. There was no edema. The peripheral arteries were patent. The blood pressure was 120 systolic and 80 diastolic. On fluoroscopy of the chest the heart was small and elongated, and the pulsations were normal. The temperature, white blood cell count, urine, sedimentation rate, circulation time and vital capacity were normal. The electrocardiogram, too, was entirely normal (fig. 1). However, the exercise tolerance test showed a definitely abnormal rise in pulse rate and blood pressure.

The electrocardiogram was repeated after exercise and presented characteristic changes of coronary insufficiency (fig. 1). The control record was entirely normal (fig. 1) with RS-T segment very slightly elevated in lead 2. Immediately after the climb of the required number of steps, the RS-T segment became depressed in the three standard leads, the depression reaching 3 mm. in lead 2. Five minutes later the configuration was the same as that prior to the test. On another occasion the patient was given 7 mm. of adrenalin subcutaneously. This produced severe precordial pain and changes in the electrocardiogram similar to, but even more marked and more persistent than those produced by effort. Smoking several cigarettes also resulted in depression of the RS-T segment.

DISCUSSION

Although the history in this case was typical of angina pectoris due to coronary artery sclerosis, at first the only confirmatory evidence of cardiac disease was the abnormal response to exercise. The fact that the physical examination, blood pressure, routine electrocardiogram and cardiac size and pulsations were normal raised a doubt in the minds of some that the pain was cardiac in origin. This doubt was dispelled by the changes in the electrocardiogram after exercise. In this patient the coronary circulation was sufficient at rest, but not during effort. It is noteworthy that the exercise produced changes in the electrocardiogram but not precordial pain. On the other hand, a patient may complain of pain after a number of climbs, yet the electrocardiogram may remain unaffected. Other authors, too, have observed the frequent independence of these responses to exercise.

It should be emphasized that the electrocardiographic alterations following exercise, as in any form of coronary insufficiency, consist of depression of the RS-T segment and lowering or inversion of the T-waves. The RS-T interval does not become elevated except very rarely (2), and changes in the QRS complex and Q waves do not appear, in contrast with these characteristic alterations in cases of coronary occlusion. In this way coronary insufficiency and coronary occlusion can usually be differentiated in the electrocardiogram (8).

Since the electrocardiographic changes following exercise are evanescent, disappearing as a rule within five minutes, it is essential that the electrocardiogram be taken immediately after completion of the exercise. The rapid disappearance speaks for a temporary ischemia and against any

permanent change to the heart muscle. In our experience the test has been without danger to the patient; when pain has occurred, it has been transitory, and not associated with other untoward symptoms. The two-step test used by us is particularly valuable in this respect, since it enables one to judge beforehand how much work each person should perform. In addition, it is a quantitative test as well as a qualitative one.

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PSYCHIATRIC PROBLEMS IN THE MEDICAL CLINIC

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The emotional reaction of a patient to his illness is important from the standpoints of diagnosis, therapy and prognosis. In the relatively acute medical conditions seen on the wards, an unfavorable attitude due to the personality of the patient can frequently be overcome by the utilization of some or all of the hospital facilities such as medication, nursing and house staff supervision. For instance, the severe diabetic patient who has neurotic fears connected with insulin therapy will not miss his injection while he is on the ward, but once home again, the neurosis may interfere with therapy to a dangerous degree. A very different problem is that of the patient coming to the Out-Patient Department for treatment. He usually suffers from a chronic ailment and must continue to take the responsibilities of daily life while under treatment. A diagnosis must be made in the face of environmental difficulties, the significance of which is frequently unrecognized by both physician and patient. Therapy must be carried on in spite of the counter-suggestions of the patient's family and friends. With this in mind a fairly large series of cases were studied in the First Medical Clinic of The Mount Sinai Hospital during 1939 and 1940, and the following is a brief summary of the psychiatric observations.

One large group includes patients best classified as therapeutic failures. These people have a definite organic disease of a curable nature but they do not, for one or more reasons, get well. Perhaps they are unable to cooperate because of environmental conditions. An example of this is a woman whose medical state requires her to rest most of the time whereas her economic resources necessitate her doing all the housework for a large family. Other reasons for lack of cooperation are inability to understand directions or emotional factors in the patient's personality. The following case illustrates the importance of understanding the factors responsible for a "therapeutic failure."

CASE REPORTS

Case 1 (35-5927). L. M. is a 48 year old white housewife who has been treated in various clinics since 1935 for complaints of abdominal pain, frigidity and frequent sore throats. A diagnosis of umbilical hernia was made and operation advised. The surgeon told the patient that operation would be postponed until she had lost weight and she was given a diet. She did not follow this diet and said that she would not do so. At this point several methods of dealing with the problem present themselves. The physician can tell her that she will not get well if she does not

cooperate, that he will refuse to treat her unless she follows his advice, or he can attempt to discover the reasons for her behavior. Practically, refusal to treat a patient is a solution of the physician's problem not the patient's, for a patient discharged from one hospital can always go to another. In this case, a psychiatric interview revealed the fact that the patient was depressed, had episodes of confusion and forgetfulness and often contemplated suicide. She greatly feared an abdominal operation and believed that the doctor would find another way to treat the hernia if her obesity prevented surgery. When an attack of tonsillitis occurred, she reacted to it ambivalently. She feared that the infection would cause her to lose weight and so bring nearer the threat of laparotomy. On the other hand, she welcomed the tonsillitis in that tonsillectomy was advised, and she believed that this operation would pacify the surgeon so that he would no longer suggest laparotomy. It is obvious that this patient's inability to get well was influenced by her emotional state. Rather than risk an acute postoperative psychosis in this case, it was decided that palliative treatment by means of an abdominal belt would be the best course to pursue for the time being.

Another problem is that represented by the patient who, in accordance with all objective standards, has been cured of an organic disease, but who persists in his original complaints.

Case 2 (34-17843). J. T., an Italian laborer, received a laceration of the chin while working on a WPA project. Following emergency treatment by a layman, he was given medical care at a hospital until discharged by the doctor as completely cured. He became convinced that he would be disfigured for life because of the carelessness and lack of interest of the physicians and became so obsessed with the scar on his chin, visible only to himself, that he refused to return to work and spent all his time looking at himself in the mirror. He had many plans for revenge on the WPA and on the physician who had "mistreated" him. A combination of social adjustments and psychotherapy have made it possible for this patient to return to work and make a social adjustment for the present in spite of the symptoms of early psychosis.

A third type of patient is the one who complains of many physical symptoms but reveals no obvious manifestations of organic disease. Such patient rarely has insight and is a problem to the administrators, the physicians including the psychiatrists and to himself. He represents a large number of the patients who attend medical clinics. The function of the psychiatrist here is to give him sufficient attention and sympathy to prevent him from wasting time and using the facilities of other clinics. Many a patient of this type would not have reached this stage of dispensary vagrancy had his emotional make-up been investigated when he first sought medical aid.

Case 3 (38-8502). F. K., a 17 year old girl had been subjected to a right ovariectomy and appendectomy at 12 years of age, and a partial left oophorectomy at 13 years for symptoms of menorrhagia, dysmenorrhea and abdominal pain. At present, the same symptoms are being treated by injections of testosterone propionate without evidence of improvement. Because of the need to attend clinic daily, this girl was forced to leave school. She has developed signs of virilism and has a hysterical paralysis of the right hand which prevents her from engaging in any useful activity. She is now doomed to the unhappy life of a chronic neurotic.

Psychotherapy can no longer be effective in view of the eloquent support being given to her neurotic symptoms by the constant organic treatment which she has been receiving for many years.

Two more groups of patients are seen by the psychiatrist in the Medical Clinic for purposes of diagnosis and disposition. These are neurotics who are aware of a need for psychiatric help and psychotics in various stages of their mental illness.

Finally, there is a group of patients suffering from diseases which are so frequently associated with personality disturbances justifying the now fashionable term "psychosomatic disease." These patients have certain traits in common. The premorbid personality in each case is that of an individual who is generally at odds with his environment but who makes little or no effort to do more than complain about it. The precipitating cause of the somatic illness in each case is some rise in tension usually due to some new "situational" force. The patient converts this anxiety into somatic symptoms and thus finds some relief of tension. The important therapeutic problem in such an instance is to reduce the patient's anxiety so that he will not find somatic illness the most desirable refuge from his conflicts and so will not be tempted to remain ill because of the "secondary gains." The importance of this group from the standpoint of furthering medical knowledge is so great that it will be discussed in greater detail than any of the others. Examples include cases of hypertension, arthritis, menopause, hyperthyroidism and bronchial asthma. Only the main psychopathological features, however, will be presented.

Case 4 (33-6731). J. K., a woman whose blood pressure was 210 systolic and 120 diastolic was married to a man who treated her cruelly. She had wanted to leave him many times but remained in order to have a home for her children. The difficulties involved in obtaining a legal divorce distressed her greatly and she alternated between being willing to put up with her husband's behavior and fighting it out in court. Each new quarrel brought on a hypertensive crisis for which she received the sympathy of her husband and at least temporarily, more humane treatment.

Case 5 (38-6649). A. B., a woman aged 40 years suffered from chronic rheumatoid arthritis, and cervico-dorsal spondylitis. She was married for the first time at the age of 38 years to a widower with a 7 year old child. She had always made a good living as an operator but feared the prospect of a lonely old age. She never loved her husband but became very much attached to his child. At first she had to live frugally and could not go to work because the child needed her constant care. In addition, economic circumstances forced her to share her apartment with a sister-in-law who took advantage of her in many ways. She had her first attack of "arthritis" following a violent quarrel with her husband over some problem in child-training. Since that time, she has had migrating pains almost constantly. She volunteers the opinion that if she had less "aggravation," she would have less pain. She refuses to consider the possibility of going to work on the ground that her earning power is greater than that of her husband and that her working would make him tend to shirk his responsibility toward his family and thus defeat the only purpose of the marriage that she had ever considered. The severity of her pain has been directly proportional to the degree of anxiety present at any given time.

Case 6 (39-552). Y. L., a 42 year old housewife who had suffered from moderate hypertension for many years, recently developed irregular menses, hot flushes, anxiety and crying spells. She became weak, refused to get out of bed and threatened suicide. Following a course of treatment with estrogenic hormone suppositories, she improved sufficiently to be able to attend the clinic for psychotherapy. An underlying cause for her anxiety was her husband's impotence, which represented the uselessness of the old age which she herself would have to face. She reacted to this with a resentment expressed by, "He should have remained strong so that he could take care of me. We can't both get old and sick at the same time for there is no one to take care of us."

Case 7 (39-7570). L. S., a 36 year old housewife complained of dizziness, nausea, insomnia and hayfever. Except for obesity, a transient acute sinusitis and a strabismus of the right eye which the patient had had since childhood, she was found to be in good health. A few months later, she began to complain that stationary objects seemed to be moving toward her. Examination was negative but a surgical correction of the strabismus was performed. A week after the operation, she was referred to the psychiatrist because she had frequent crying spells, refused to remain alone, feared to cross streets, and had attempted suicide. The temporary loss of vision had forced her to think of her problems more intensively. There was a long history of marital discord, an illegitimate but much-loved child who had been taken from her by the Children's Court, an irresponsible lover and financial stress. While waiting to go to a convalescent home, she developed her first attack of bronchial asthma. This was followed by such frequent and severe attacks that she required immediate hospitalization.

Case 8 (38-3468). H. S., a 50 year old man was subjected to a subtotal thyroidectomy one year ago, because of increasing nervousness, tremor, weight loss, sweating, palpitations and a basal metabolic rate of 49 per cent. One month ago, he had a recurrence of the same complaints but the basal metabolic rate was not elevated. He gave a history of long-standing marital discord and of difficulty with his children, but said that since he had been ill, his wife had become a different woman. Whereas she had previously been nagging and antagonistic, she was now sympathetic and considerate. However, he claimed that she was not intelligent enough to understand that he would never be cured so completely that he would be able to bear the old bickering. It was after a quarrel with her that he had his recent attack.

DISCUSSION

The set-up of the Medical Clinic limits the psychiatrist in various ways which must be understood in order to obtain a fair evaluation of the results of psychotherapy. Both the limited time allotted to each patient and the lack of privacy for discussion make intensive psychotherapy almost impossible. Under these circumstances, the psychiatrist must be satisfied in many instances with the opportunity to reach a diagnosis and leave the therapy in the hands of social workers and other more or less experienced and willing individuals.

In view of these difficulties, the most practical therapeutic approach has been found in the recognition and treatment of the "secondary gains" from the illness rather than the disclosure of the root of the emotional problems presented by the patient. An answer to the following questions should be sought in each case:

1. What advantage does the patient gain from being ill?
2. Does this advantage compensate for the discomforts of the illness?
3. What part has the environment played in the development of this illness, and what part does it play in maintaining the neurotic status?
4. Can the environment be changed in such a way that the secondary gains from illness are less than those in health?
5. From a realistic standpoint, is the neurosis actually the best form of adjustment to an intolerable, but unalterable environment?

Throughout such an investigation it is important to bear in mind the total personality structure of the patient and to realize the great difficulties involved in altering this personality by the rather superficial form of psychotherapy employed under the circumstances.

These patients would not have developed neurotic difficulties had they been capable of dealing effectively with the problems in their lives. Many of them have found that the difficult environments which they were forced to cope with became less painful when the illness developed. A formerly inconsiderate husband was sympathetic when his wife became ill. It is only natural for such a woman to prefer to remain ill and keep her husband sympathetic. A useful therapeutic approach in such circumstances is to offer the coveted reward for health rather than for illness. In the example just mentioned, a frank discussion with the husband may make it clear to him that a considerate attitude toward his wife will prevent her from getting sick and be of great practical advantage to him.

The majority of these patients feel neglected by the world around them and are often helped merely by a manifestation of interest on the part of the physician or hospital. If they can be made to understand that the interest will be maintained when they are well, it is a strong incentive toward recovery. It must also be understood that this interest must be in a tangible form to be acceptable just as a child must be rewarded for good behavior by candy rather than promises of future joys. For this reason, physiotherapy, rest in a convalescent home, and other such procedures frequently can be used as a reward for good health rather than in the treatment of actual pathological conditions. From a purely economic point of view, it may be said that a sojourn in a convalescent home for a week is really a good investment if it can be substituted for the exceedingly expensive and misdirected treatment of the patient's need for attention which takes the form of diagnostic procedures.

It is generally impossible to make these patients completely independent of some form of therapy. The next best end-result is to shift such dependence to the psychiatrist rather than to the illness. This is most successfully accomplished by the psychiatrist consciously striving to maintain the role of the good parent to the patient, listening sympathetically and finding some way of improving the relationship between the patient and the environment.

CLINICAL PATHOLOGICAL CONFERENCE

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

Wednesday, November 1, 1939

Mercury Nephrosis due to Mercurial Diuretic (Mercupurin). Rheumatic Cardiovalvular Disease (Mitral and Aortic Insufficiency). Arterial Hypertension.

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

History (Adm. 438460; P.M. 11131). (First Admission. May 31, 1938). The patient was a twenty-six year old German refugee. Sixteen years ago, at the age of ten, he had a peritonsillar abscess which required incision. This was followed by migratory polyarthritis. Eleven years ago he had an attack of scarlatina. Ten years ago he again developed a severe tonsillitis, which was followed by a febrile illness during which the heart was said to have been involved. Four weeks before admission he developed a dull ache in the left chest. Nevertheless, he was able to work until two days prior to admission when the pain became more severe and was accompanied by fever.

Examination. He was fairly well developed, poorly nourished, and appeared acutely ill. Temperature was 102°F. The lungs were clear. The heart was markedly enlarged. Systolic and distolic murmurs were audible at the apical and aortic areas. P^2 was louder than A^2. There were numerous ventricular extrasystoles. The blood pressure was 166 systolic and 10 diastolic. The peripheral manifestations of aortic insufficiency were present.

Laboratory Data. Hemoglobin, 76 per cent. White blood cells, 32,700 with 84 per cent polymorphonuclear leucocytes. Sedimentation time, 18 minutes. Venous pressure, 11 cm. with a rise to 13 cm. on right upper quadrant pressure. Saccharine time, 45 seconds. The urine concentrated to 1.036 and contained 2 plus albumin on one occasion and a trace on another with occasional casts. The blood Wassermann reaction was negative. Electrocardiogram showed a marked left ventricular preponderance, prominent P waves and slurring of the QRS. A roentgenogram of the chest showed a marked generalized enlargement of the heart, suggestive of a combined mitral and aortic lesion.

Course. An increased sedimentation rate and tachycardia as well as a sub-febrile course persisted. Evidences of progressive heart failure developed, therefore, the patient was digitalized. In addition, he was given one injection of mercupurin. Congestive heart failure rapidly cleared and his general condition improved. One month before discharge the blood pressure was found to be more than 300 systolic, while no diastolic pressure could be recorded. The urine concentrated to 1.026 and showed a trace of albumin. At the time of discharge (August 22, 1938) his venous pressure was 6 cm. and the heart appeared to be somewhat enlarged. The blood pressure was 300 systolic and 0 diastolic.

Second Admission. (April 5, 1939). Up to seven weeks prior to this admission the patient had been feeling relatively well, with no symptoms of impaired cardiac reserve. In fact, he had even resumed work as a shipping clerk, but then he developed a sensation of abdominal pressure and swelling of the thighs. He was told he had developed abdominal fluid and this was treated by six mercurial diuretic suppositories in the space of three and a half weeks. The further administration of suppositories was stopped because of the discovery of marked albuminuria. During the past two weeks his ankles have become swollen. For three days he has had generalized muscle aches.

Examination. On examination the patient was dyspneic, orthopneic, had markedly flushed cheeks, and a deep cyanosis of the lips. Resonance was impaired at the right lung base below the angle of the scapula. The heart findings were essentially the same as on the first admission, i.e. it was markedly enlarged, systolic and diastolic murmurs were heard at the apical and aortic areas and signs of aortic insufficiency were prominent. The blood pressure was 190 systolic and 0 diastolic. The patient was markedly edematous below the waist. Shifting dulness and a fluid wave were elicited in the abdomen. The genitalia were also edematous. The liver was felt 3 cm. below the costal margin. The neck veins were moderately distended. The nail beds were markedly cyanotic.

Laboratory Data. Hemoglobin, 106 per cent. White blood cells, 13,600 with a normal differential. The urine showed a casual concentration up to 1.022, 3 plus albumin and an occasional granular cast. Blood urea nitrogen was 19 mg.; sugar, 100; cholesterol, 320; total protein, 5.7 per cent with albumin of 4 per cent and globulin of 1.7 per cent. The Wassermann reaction was negative. Venous pressure was 25.5 cm. with a rise to 27.5 cm. on right upper quadrant pressure. Saccharine time was 43 seconds. Sedimentation time was normal.

Course. Because of the marked albuminuria and massive edema, associated with the use of mercurial suppositories, the possibility of a mercurial nephrosis was entertained. However, in view of the good concentrating function of the kidneys, the normal level of the blood urea nitrogen, and the unmistakable signs of congestive heart failure, it was deemed advisable to treat him cautiously with mercupurin. On the day of admission he received one injection of mercupurin. On the third day of hospitalization he developed drowsiness, perspiration and rapid, shallow respirations. The temperature rose to 101°F. Although the symptoms and signs were those of shock, the blood pressure remained at 200 to 300 systolic and 0 diastolic. He was immediately placed in an oxygen tent. A few hours later he complained of severe "tearing" epigastric pain. He was treated with nitroglycerine which decreased his pain and appeared temporarily to lower his blood pressure after two doses to 110 systolic and 40 diastolic. A cephalic vein thrombosis also occurred. The blood urea nitrogen now was 42 mg. per cent. The patient continued to be extremely cyanotic even in an oxygen tent. The systolic blood pressure rose again during the next few hours above 300 so that it could not be determined with the monometer. His temperature rose to 104°F. He died (April 11, 1938) four days after admission with a clinical picture of combined myocardial failure and renal insufficiency.

Necropsy Findings. Dr. Klemperer. The left ventricle of the *heart* showed marked dilatation and hypertrophy. The chief valve changes were on the aortic valve. Here the cusps were rolled in, the edges thickened, and reduced to only one-half its usual size. The mitral valve showed only moderate changes. There were no recent lesions in the myocardium or the valves. The *liver* showed much congestion and centro-lobular necrosis. The *lungs* were congested and there were some areas of pneumonia. The *kidneys* were slightly enlarged and gray in color. There was a considerable degree of degeneration. Microscopically, the glomeruli appeared normal. The tubulae, however, were the seat of severe degeneration, and in some

areas even necrotic. In addition there was calcification in some of the tubules. The *intestine* showed a distinctly hemorrhagic area. Chemical analysis revealed the presence of mercury in the kidneys.

Comment. Dr. Klemperer: The localization of the renal pathological changes, particularly with associated calcification in the tubules, together with the intestinal changes, are most suggestive of mercury poisoning. In addition the demonstration of mercury in the kidney by appropriate chemical analysis appears to further bear this out.

Dr. Baehr: The occurrence of severe renal injury incidental to the use of mercurial diuretics is certainly contrary to the general experience with this therapeutic ally. I have treated patients with mercurial diuretics every fifth day for seven and a half years without any significant albuminuria or other signs of renal irritation. If such accidents do occur, they must be extremely rare. There is one other possible explanation for the postmortem. In addition to the increased output of fluid induced by the diuretic, there is an increased output of sodium chloride which may at times be great enough to produce symptoms, such as cramp-like pains in the extremities. If, in addition, there is superimposed vomiting, an actual alkalosis may occur. As Haden and Orr have demonstrated, alkalosis may produce severe damage to the convoluted tubules with calcification; a pathological picture that can not with certainty be differentiated from the picture of mercury poisoning. Dr. Zeman has reported upon the difficulty in differentiating between the renal damage due to alkalosis and that caused by mercury and bismuth.

Dr. Jerome Kohn: The danger of the use of mercurial diuretics in lipoid nephrosis should be pointed out. Sudden exitus may follow its administration in this condition.

Dr. Ernest Pick: I should like to comment on the historical development of the use of mercury in medicine as a diuretic agent. It is well known that calomel (mercurous-chloride) was used in cardiac dropsy as far back as the eighteenth century. Some sixty years ago this remedy was rediscovered by Jendrassik who administered it with great success. The results obtained were better than with digitalis or caffein. The urine secretion often increased to 7 or 8 liters a day and the urinary content of urea and chlorides also became greater. These results, for the most part, were not present in cases of ascites secondary to hepatic cirrhosis. In nephritic edema, calomel either produced no striking effect and often aggravated the underlying condition. Bowel regulation was effected by the use of opium. This combination of calomel and opium is still popular on the Continent. Today, however, the dangers of calomel are well recognized, particularly the not infrequent production of mercury poisoning. The introduction of organic mercury compounds was made by P. Saxl. They are much more powerful than any other diuretics. Their chief advantage lies in their relative solubility, permitting their use intramuscularly, intravenously, and

even intraperitoneally. The average content is 40 per cent mercury in non-ionized form, administered in 10 per cent solutions. It is particularly noteworthy that the diuretic effect is increased if a mild acidosis is present. This is obtained by the use of such salts as ammonium chloride, calcium chloride, etc.

The first such compound was Novasural Merbaphen, a combination with Barbitone. Toxic effects were not rare, and it was soon displaced by salyrgan. The third preparation, Novurit or Mercupurin, is the most powerful and least toxic. It is a combination of a 10 per cent solution of an organic mercury compound with a 5 per cent solution of theophylline. Serious accidents are very rare. Another mercury compound of recent introduction is Esidrone. It may be used in doses of 1 or 2 cc. by intravenous injection. The fifth preparation, Mercurin, differs from the other compounds by reason of its relatively slight solubility. It is, therefore, used in the form of suppositories.

It should be stressed that the precautions necessary in the use of calomel apply equally well to all the organic mercury compounds. The chief contra-indication is nephritis. From the pharmacologic and clinical point of view it is quite remarkable that the effect is largely dependent on the state of the liver. Jaundice and hepatic cirrhosis usually inhibit the action of these drugs. The experimental investigations bear this out. An important point is the fact that with the diuresis there is a greatly increased secretion of sodium chloride. It is conceivable that in some cases the diuresis actually ceases because of this. In such cases diuresis can be started again by the administration of sufficient amounts of saline.

Reported by *Max Ellenberg, M.D.*

Carcinoma of the Adrenal Cortex in a Man of Forty-four Years

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

History (Adm. 446951; P.M. 11291). The patient, a man of forty-four years, was admitted to The Mount Sinai Hospital Private Pavilion on October 9, 1939. A year and a half before admission he noted extreme nervousness and at about the same time noticed that his urine was blood tinged. His private physician informed him that he had a systolic blood pressure of 200 and that he had blood in his urine. Since the onset of his symptoms eighteen months ago he had suffered from intermittent attacks of right upper quadrant pain. In addition to these complaints he has had insomnia, loose bowel movements and a weight loss of ten pounds. Two months before admission a cholecystectomy and appendectomy were done in another hospital because of persistent right upper quadrant pain. The operation did not relieve his symptoms and he entered this hospital for further investigation.

Examination. The patient was a well developed and nourished white man who did not appear acutely ill. His blood pressure was 186 systolic and 118 diastolic. The heart was enlarged to the left anterior axillary line. A well healed upper right rectus scar was present. The abdomen was definitely tender in the right upper quadrant and there was a smooth firm mass occupying most of this area. The peripherhal arterial pulsation was very marked and the radial pulse could be clearly seen at the wrist. The clinical impression was renal or suprarenal tumor.

Laboratory Data. The hemoglobin was 78 per cent (Sahli); red blood cells, 4,390,000; white blood cells, 7,550 with a normal differential count. The blood urea nitrogen was 8 mg. per cent. The urine showed a faint trace of albumin and an occasional red blood cell, white blood cell and hyaline cast. An intravenous pyelogram revealed a definite depression of the upper pole of the right kidney with elongation of the middle calyceal system.

Course. A perirenal insufflation of air to visualize the right kidney and adrenal was attempted. This was abandoned, however, because the needle struck blood on three different attempts and the danger of air embolism was considered too great to warrant the procedure. Operation was performed three days after admission. The abdomen was first explored through a right rectus incision. A mass the size of a football was found situated at the upper pole of the right kidney. It was adherent to the kidney below and to the liver above. This incision was closed and the patient then placed on his left side and a routine oblique incision made to expose the right kidney and tumor. The tumor mass was explored by palpation. Because of its extreme size and vascularity, it was deemed inoperable and the operation was discontinued. One day after operation, the patient's temperature rose to 108.6°F. The pulse became rapid, weak and irregular. The urinary output dropped to 7 ounces in twenty-four hours and a renal shutdown was suspected secondary to the trauma suffered at operation. Emergency restorative measures were instituted. The blood pressure dropped to 50 systolic and over 30 diastolic, and the patient died shortly afterwards.

Comment. Dr. Klemperer: This very large tumor is *adrenal* in origin. The *kidney* is compressed by the growth, which is in intimate relation to the inferior vena cava, invading it at one point. It is of interest to note that despite the venous involvement there were few metastases only in the *liver* and *lungs*. The tumor has large areas of hemorrhage which may have been caused by the previous aspirations. It is for the most part yellowish, and in some areas necrotic. This is the typical appearance of an adrenal cortical carcinoma. Microscopically the tumor was composed of densely arranged cuboidal cells. They were highly irregular, their appearance consistent with the diagnosis of adrenal cortex carcinoma. The most common types of adrenal neoplasm can be classified as either originating in the cortex or in the medulla. The former, mesodermal in origin, are either adenomas or carcinomas. The latter which spring from the ectodermal portion of the glands, are divided into sympathicoblastomas and pheochromocytomas. The sympathicoblastomas are of varying degrees of maturity. The most immature tumors are highly malignant and chiefly occur in infancy, occasionally in the new born eve. The most mature forms are the ganglioneuromas which may grow, to become very large encapsulated retroperitoneal neoplasms without forming metastases. They

are more frequent in adult life. The pheochromocytomas are derived from the specific cell of the adrenal medulla which contains chromophile granules and is assumed to take part in the manufacture of adrenalin. These tumors are generally encapsulated and remain localized, but a few have been reported with metastases. They are biologically active tumors causing symptoms of paroxysmal hypertension. Several cases have successfully been operated upon, one recently reported by E. Beer, King and Oppenheimer.

Dr. Baehr: This male patient did not have characteristic clinical findings of the "Cushing Syndrome." It is hardly to be expected that the masculinizing effect of a neoplasm of the adrenal cortex could be recognized in a male. The only significant clinical effect of the tumor in this case was the persistent arterial hypertension.

Reported by *Abner Kurtin, M.D.*

CLINICAL NEUROPATHOLOGICAL CONFERENCE

JOSEPH H. GLOBUS, M.D., *presiding*

Monday, March 25, 1940

Case 5[1]. Subarachnoid Hemorrhage, Due to Ruptured Aneurysm

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

History (Adm. 413991; P.M. 10515). An instructor in physical training, 31 years of age, was admitted to the hospital for the first time on August 20, 1937. Two months previously, he passed through an episode of sudden chilliness and generalized weakness, to be followed on the next day, while bending over, by sudden severe pain at the back of his head. This pain persisted for several days. He was seen by a physician who treated him for sinusitis, with the result that after several treatments his headache disappeared. He remained apparently well for about six weeks when on August 2, while performing calisthenics the headache suddenly returned accompanied by a feeling of faintness and stiffness of the neck. His condition during the next eleven days is not known, but at the end of that time, severe attacks of headache set in and while exercising on August 13, he suddenly lost consciousness for a few minutes. On regaining consciousness, he felt severe pain in the front and top of his head. He was treated by several physicians and all of them treated him for sinusitis. At first he seemed to improve, but on the day before admission severe headache and stiffness of the neck returned and persisted.

Examination. The patient appeared acutely ill. He was slightly drowsy, but cooperative. There was slight tenderness over the frontal and ethmoid sinuses. A naso-pharyngitis was present with a mucopurulent postnasal discharge. His head was held slightly retracted, the neck was stiff, and a Kernig sign was obtained bilaterally. The spine was also rigid and displayed muscle spasm. The blood pressure was 118 systolic and 72 diastolic.

Laboratory Data. Cerebrospinal fluid: xanthochromic; initial pressure, 140 mm. of water; cells, 8700 red blood cells and 650 white blood cells (64 per cent polymorphonuclear leucocytes) per cu. mm.; smear, no organisms; culture, negative; sugar, 15 mg. per cent; chlorides as sodium chloride, 640 mg. per cent; total protein, 108 mg. per cent. Blood: white blood cells, 17,200 per cu. mm. of which 74 per cent were polymorphonuclear leucocytes. Other blood examinations, including the Wassermann reaction were normal as was the urinalysis. X-ray examinations of the sinuses and of the spine were reported as negative.

Course. A diagnosis of subarachnoid hemorrhage and sinusitis was made. An

[1] The first four cases were presented in a previous issue of the Journal (Vol. VII, No. 5).

otolaryngological examination on the day of admission revealed a mucopurulent discharge after irrigation of the ethmoid sinuses. Because of the high proportion of leucocytes in the spinal fluid, it was felt that the sinusitis was a partial, contributing factor in producing the meningeal irritation. A bilateral sphenoethmoidectomy was performed under local anesthesia. Empyema of the right sphenoid was found together with a left sphenoiditis, an osteoma, and bilateral ethmoiditis. A culture of the pus showed B. coli and Staphylococcus albus. A biopsy of the mucous membrane was reported after pathological study as showing no significant changes. During the patient's nineteen day stay in the hospital the stiffness of the neck and the headache gradually diminished and he was asymptomatic at the time of his discharge.

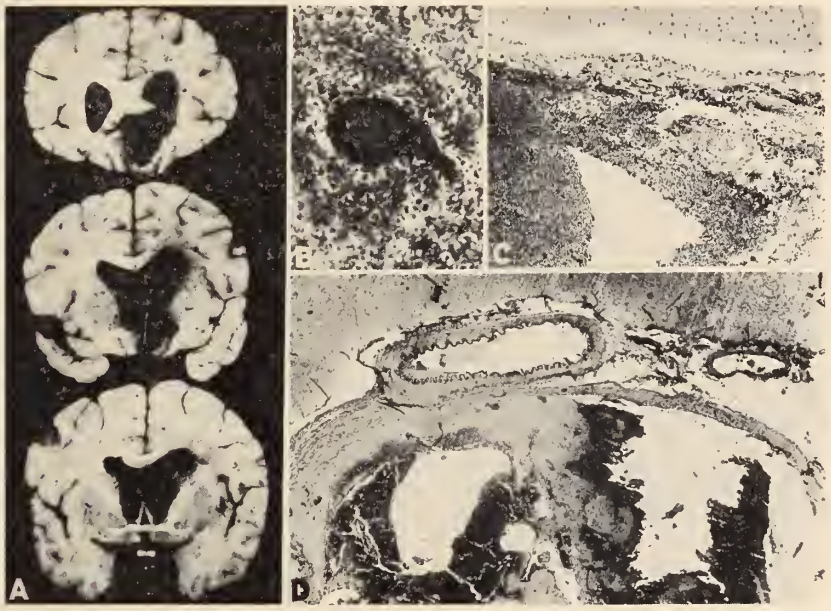

FIG. 7. Case 5. A. Coronal sections showing blood in the lateral ventricles continuing through a defect in the grain tissue with the blood in the subarachnoid space.
B. Area of softening showing a naked blood vessel, (photomicrograph, hematoxylin and eosin stain).
C. Ventral portion of medulla oblongata showing blood elements in the subarachnoid space, (photomicrograph).
D. Right anterior cerebral artery (aneurysmal part) within which there is an organized and fairly recanalized thrombus, (photomicrograph, Van Gieson stain).

His first four days at home were spent in bed and were uneventful, but on the morning of the fifth day he was awakened by headache and five minutes later passed through a convulsive episode. He was brought to the hospital two hours later.

Examination (Second Admission, September 13, 1937). The patient was confused and spoke incoherently. His blood pressure was 90 systolic and 60 diastolic. The pulse rate, 55 per minute; the temperature 96.4° F.; respirations, 16 per minute. He displayed stiffness of the neck and bilateral Kernig signs. Both discs were slightly blurred. The pupils were small, but he had received morphine shortly before admission. All the deep tendon reflexes were considerably depressed. There was no response to plantar stimulation.

Laboratory Data. Cerebrospinal fluid: bloody; initial pressure, 340 mm. of water.

Course. Three hours after admission, the patient became comatose. Occasional convulsive movements of the upper limbs occurred. The pulse and respirations gradually became slower and he finally ceased five and a half hours after admission, about seven hours after the onset of his last episode.

Necropsy Findings. Brain. Gross. There was a mass of clotted blood covering the midbrain, pons, and medulla and totally obscuring the structures at the base of the brain. On sectioning the brain, a circumscribed area of softening into which hemorrhage had occurred was found directly beneath the genu of the corpus callosum, close to the lip of the anterior ventral extension of the dorsal longitudinal fissure (fig. 7A). It occupied almost the entire vertical axis of that part of the brain and extended laterally for about one centimeter. This area, traced backwards, was found to communicate with the right lateral ventricle through a defect in the floor of the right anterior horn. From here the hemorrhage could be traced through the entire ventricular system.

The ventricular system was considerably enlarged and symmetrically so except for the anterior horn on the right side which was disfigured and displaced. Near the posterior aspect of the anterior commissure in the ventral extension of the dorsal longitudinal fissure, there was an area of organization outlining what was probably the anterior cerebral artery.

Microscopic. The gross area of hemorrhagic softening shows practically complete replacement of the nervous parenchyma by red blood cells. A few irregular islands of brain tissue remain. Naked blood vessels were found in the softened area (fig. 7B). The cerebral tissue adjacent to this zone is infiltrated with collections of red blood cells. A section through the medulla revealed a large area of hemorrhage on its ventral surface (fig. 7C). The subarachnoid space was crowded with extravasated blood and the leptomeningeal vessels congested with red blood cells. Serial sections of tissue enclosing the right anterior cerebral artery, stained by the Van Gieson method, show the vessel to be markedly widened and its lumen partially filled with an organized thrombus (fig. 7D). The intimal lining for the most part could not be distinguished, and the internal elastic lamina was absent. The media displayed disorganization of its structure and in places was very much thinned out.

Comment. Dr. Globus: It is highly probable that the initial clinical manifestations were precipitated by some oozing from the aneurysm which was subsequently found at autopsy. The sinusitis which was diagnosed repeatedly, may have contributed something to the clinical picture but whatever its contribution it has helped to mislead rather than to guide to a correct diagnosis. The presence of xanthochromic cerebrospinal fluid and the high red blood cell count on his first admission should have affirmed the diagnosis of spontaneous subarachnoid hemorrhage, in spite of the tenderness over the accessory nasal sinuses and the presence of a mucopurulent postnasal discharge. The exploration of the sinuses, somewhat hazardous under the circumstances, though it resulted in some positive findings, should have been avoided. The improvement in the following three weeks which may have been regarded at first as justifying the surgical intervention must be reinterpreted in the light of subsequent events. The abrupt interruption of the convalescence by a brief and stormy course which lead to a fatal termination is a common occurrence in ruptured aneurysms undergoing temporary healing.

The case also illustrates how an aneurysm, in this instance arising from an anterior cerebral artery, having eroded adjacent parts of the brain substance, when ruptured may lead not only to extravasation into the subarachnoid space, but also at some later time may cause hemorrhage into the ventricular system, which indeed, in this case was responsible for the fatal issue.

Reported by *M. Axelrod, M.D.*

Case 6. Transitional Glioneuroma, Hemispheric, Right

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

History (Adm. 439203; P.M. 11149). A man, 55 years of age, was admitted to the hospital on April 20, 1939. His fatal illness began about four months previously, when it was observed that he tended to move about in a somewhat "drunken" fashion, and dropped objects which he tried to hold in his left hand. One week later, while riding in the subway, he suddenly experienced a jerking of his jaw and face. The episode lasted only a few minutes. Then he asked a question of direction from a fellow passenger but was treated as if he were drunk. On attempting to leave, he discovered that he could not move his left arm and leg. With difficulty, he managed to reach home. A physician who examined him at that time told him that he had had a "stroke." For the next few days the man noticed that his speech was thick and that liquids would drool from his mouth. During the next two months he gradually improved and he considered returning to work. Then suddenly one night he was awakened by jerkings of his jaw and face. He was apparently conscious throughout the episode, for though he did not speak, he awakened his wife with one arm. His wife noticed a blinking of his eyelids and a rolling about of his eyes. Again, the attack ceased in a few minutes and was followed by inability to move the left arm and leg. This time, however, no subsequent improvement set in. In addition, his appetite became poor and he complained of generalized weakness. One week before admission he began to experience frequent frontal and occipital headaches. He noticed, too, that if he yawned he would experience pain in the knuckles of his left hand. On the day of admission, following a long automobile ride, vomiting and diarrhea set in.

Examination. The patient lay passively in bed. He would answer questions to the point although there was a perceptible delay between question and answer and words were produced slowly. He appeared to be in good contact with his environment and there was no evidence of memory disturbances. Percussion of the skull produced a dull, high-pitched note over the right parietal region. The left palpebral fissure was wider than the right. The left pupil was smaller than the right. Both discs showed papilledema with retinal hemorrhages in the left disc. Occasional twitchings of the right platysma muscle were seen. There was a left hemiparesis affecting the face, tongue, and extremities associated with hyperactive deep

reflexes, Babinski sign, and diminished abdominal reflexes, all on the left side. There was astereognosis in the left hand. Pulse rate, 64 per minute. Blood pressure, 100 systolic and 75 diastolic.

Laboratory Data. Cerebrospinal fluid: clear, colorless; initial pressure, 140 mm. of water; Ayala index, 3.5: dynamics, normal; cells, 0; Pandy, trace; total protein, 54 mg. per cent; Wassermann, colloidal gold, and globulin tests, negative. An x-ray examination of the skull was reported as normal. Blood and urine examinations were essentially normal.

Course. The diagnosis of an expanding lesion in the right fronto-parietal region of the brain was made, probably primary, possibly multiple and possibly metastatic. An electroencephalography confirmed the location of the lesion. A pneumoencephalography was attempted but proved to be unsuccessful for apparently no air entered the ventricles. Following this procedure the patient became somnolent and his temperature became elevated (101.8°F.). The following day he passed into a semi-stuporous state and incontinence of urine set in. A lumbar puncture at this time yielded xanthochromic, slightly turbid cerebrospinal fluid at a pressure of 300 mm. of water. It contained numerous red blood cells and 120 white blood cells per cubic millimeter of which 90 per cent were polymorphonuclear neutrophils. The patient's failing state precluded surgical intervention. On this same day, his tenth in the hospital, the stupor suddenly deepened; he became cyanotic and died twenty minutes later.

Necropsy Findings. Brain. Gross. Coronal sections of the brain showed that the right cerebral hemisphere was enlarged to 1½ times the size of the left one (fig. 8A). Within the right hemisphere there was found an extensive area of discolored, disintegrating tissue which began about 7 cm. posterior to the frontal pole and reached posteriorly as far as the anterior third of the occipital lobe. This area varied in appearance, size, and consistency with the level of the coronal section. In the frontal lobe it was quadrilateral in shape, measuring about 3 cm. in its horizontal, and greater diameter and consisted of a peripheral zone of reddish discoloration enclosing semi-fluid reddish gelatinous substance. At a level with the head of the caudate nucleus, the area of discoloration included an area of firm, bright yellow tissue, 2 cm. wide in the horizontal plane. Grossly this appeared to be tumor tissue. Further posteriorly, a cyst about 2 cm. in diameter appeared replacing the yellowish area just described. The whole area of discoloration reached its greatest size in this posterior portion where it had replaced practically the whole lentricular nucleus and adjacent lateral brain tissue.

Both ventricles were distorted and enlarged. Peculiarly enough, the anterior horn of the right ventricle (the side of the lesion) was enlarged; its body, however, was diminished in size and somewhat depressed, increasing slightly in size in its more posterior portion.

Transverse sections through the midbrain disclosed numerous linear and circular hemorrhages which could be traced caudad into the anterior third of the pons.

Microscopic. Sections of the tumor, stained by the various neurohistological techniques, disclosed a richly cellular and vascular tissue (fig. 8B). Often there are clusters of small blood vessels, resembling a bouquet. Many vessels are outlined by aggregations of small round cells, most densely aggregated toward the vessel and apparently thinning out in the tumor tissue where they are diffusely scattered. These cells contain scanty poorly defined cytoplasm and one or two deeply staining nuclei (fig. 8C and D). Scattered among them there are neuroblastic cells. More mature appearing nerve cells are encountered in some regions of the tumor particularly where there is less cellularity and the tissue assumes the appearance of a delicate reticulum (fig. 9A), such as is seen in the more differentiated regions of the transitional glioma. Cajal gold sublimate stains (Globus modification) disclose

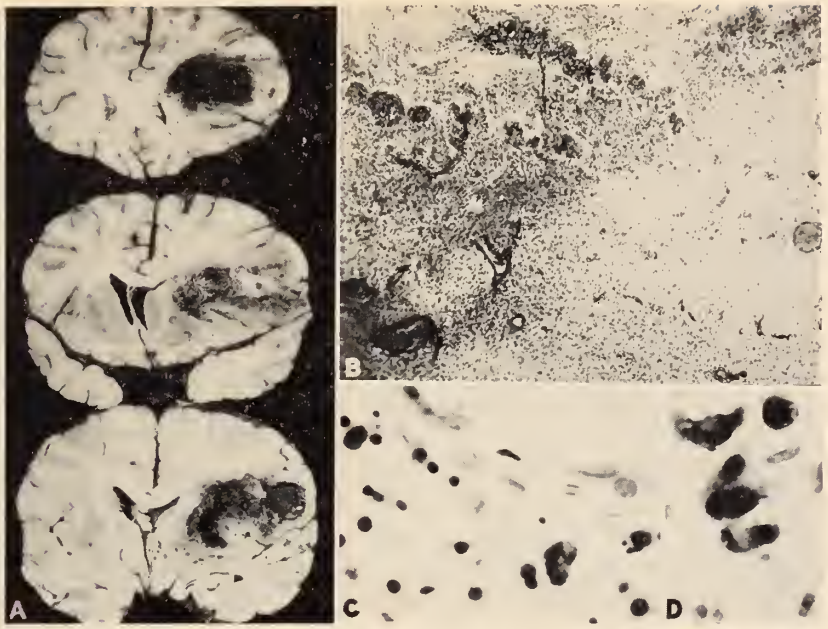

FIG. 8. Case 6. A. Coronal sections of the brain showing the extent of the tumor in the depth of the right cerebral hemisphere.

B. The general histologic appearance of the growth, (photomicrograph, hematoxylin and eosin stain).

C and D. Multinucleated giant (neuroblastic) cells, (photomicrograph, Nissl stain).

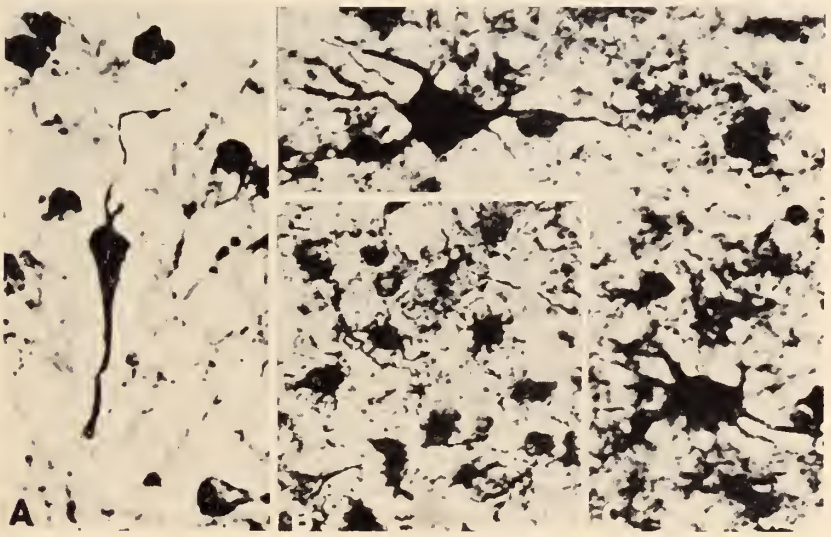

FIG. 9. Case 6. A. A fairly mature nerve cell, (photomicrograph, Bielschowsky stain).

B and C. Large, multi-processed glial cells (photomicrograph, Cajal impregnation method, Globus modification).

not only numerous short-rayed glia cells but also large atypical cells, each suggestive in appearance of both glial and neuronal elements and apparently types of hybrid cells (fig. 9B and C). Sections of the midbrain, stained with hematoxylin and eosin disclose diffuse and circumscribed extravasations of well preserved red blood cells and compression of the left half with some rarefaction and necrobiosis in the corresponding basis pedunculi.

The tumor tissue in various areas displays glial and neuronal cells at various levels of differentiation. The dominant level is between the less and the more differentiated types. This histological feature and the appearance of the blood vessels puts this tumor in the class of the transitional neuroglioma.

Comment. Dr. Globus: Of interest in this case are the occurrences of convulsive seizures early in the clinical history, their limitation to the face and jaw and the preservation of consciousness during such seizures. These features mark the attacks as Jacksonian in character and "fragmentory" in extent. It should also be noted that the cerebrospinal fluid when first examined was normal in all phases, except that the Ayala index indicated the probability of the expanding character of the lesion, though the initial pressure of the fluid was not above normal. The appearance of microscopic blood and xanthochromia in the fluid following an unsuccessful encephalography, must be attributed to this precedure and to the vascularity of the tumor.

The presence of many poorly differentiated nerve cells alongside of poorly differentiated glial elements places the tumor among the transitional glioneuromas, indicating that the tumor is not as benign as a glioneuroma nor as malignant as a spongioneuroblastoma.

Reported by *J. M. Zucker, M.D.*

Arthur Lorsch

September 14, 1873–February 4, 1941

Mr. Arthur Lorsch died at The Mount Sinai Hospital on February 4, 1941 after having served as a Trustee for thirteen years. His long period of service to the Hospital was characterized by a deep interest in the work of the clinical departments and that of the laboratories. With characteristic generosity he was always ready to assist in improving the relationship of the laboratory to the clinical services, especially if it might have an influence upon clinical teaching and scientific work.

It is perhaps unknown to most of the staff of The Mount Sinai Hospital that his support in recent years assisted materially in the conduct of the clinical pathological conferences and of the JOURNAL OF THE MOUNT SINAI HOSPITAL. It seems appropriate that we record our appreciation of his kindly interest and his loyal support. Many of us will long treasure the memory of his friendship.

GEORGE BAEHR.

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.

Role of the Uterus in the Production of Manometric Fluctuations during Uterotubal Insufflation (Rubin Test). S. Wimpfheimer and M. Feresten. Am. J. Obst. & Gynec. 37: 405, March 1939.

Observations were made on 60 living rabbits to determine whether the uterus participates in the production of the manometric fluctuations, seen during uterotubal gas insufflation.

Manometric fluctuations occurred only when tubal pateney was present.

The contractions obtained by insufflating the isolated uterus differed from those recorded during uterotubal insufflation.

When the tube alone was insufflated the contractions were similar to those obtained during uterotubal insufflation.

Excision of successive segments of uterus and tube during gas insufflation localized the power of contractility to the more muscular tubal isthmus.

During uterotubal insufflation the uterus became distended and less contractile, whereas the tube showed no marked distention and its muscle function remained unaltered.

Nature of Vegetations of Bacterial Endocarditis. A. C. Allen. Arch. Path. 27: 661, April 1939.

According to the long established current concept, the vegetations of bacterial endocarditis are assumed to be essentially thrombotic material deposited from the chamber blood as it flows over the valves. On the basis of histologic studies of differentially stained vegetations, it is concluded, contrary to this concept, that the bulk of such vegetations is derived from the fibroelastic tissue and the blood elements from necrosed valvular vessels. This view of the histogenesis of vegetations is deemed of possible importance in its reflection of the more general aspects of the pathogenesis of this disease.

Tuberculin Patch Therapy. H. Vollmer and E. Goldberger. Quart Bull. Sea View Hosp. 4: 317, April 1939.

A tuberculin patch therapy is described on the basis of the tuberculin patch test. Tuberculin in gradually increasing amounts is administered in the percutaneous way by the use of gradually increasing numbers of filter paper squares saturated with tuberculin. Indications and exact directions are given for the individual use of this therapy which is essentially a desensitization therapy. Before the treatment is instituted, an approximate determination of the skin sensitivity to tuberculin is carried out by a special allergometric tuberculin patch test. Its composition is described.

Twenty-five children with active tuberculosis were treated with the tuberculin patch therapy. No untoward effect was observed due to the tuberculin treatment. About fifty per cent of the children were improved. Further investigation will be needed to confirm the efficacy of this therapy.

The Nature of Arterial Hypertension with Special Reference to the Role of the Kidney. M. Prinzmetal, B. Friedman and D. Abramson. Ann. Int. Med. 12: 1604, April 1939.

Hypertension was produced in seventeen dogs by means of unilateral renal ischemia. Crude saline extracts prepared from the ischemic kidney had greater pressor effects than those of the contra-lateral unoperated kidney in sixteen of the seventeen experiments.

The mean pressor effect of saline extracts of kidneys from twenty-one patients who had hypertension of various types during life was greater than that of renal extracts from twenty-four subjects who had had normal blood pressures.

Vasomotor Effects of Blood in Patients with Hypertension and Animals with Experimental Hypertension. B. Friedman and M. Prinzmetal. Ann. Int. Med. 12: 1617, April 1939.

The existence of increased pressor (or diminished depressor) properties in the blood of animals with renal hypertension may be postulated on theoretical grounds.

In a variety of experiments designed to test this hypotheses no increase in the humoral pressor activity in hypertensive individuals or in animals with experimental renal hypertension was detected with the methods employed.

These included: Massive cross transfusion in humans; tests of plasma on the rabbit ear preparation; tests of whole blood by means of perfusion of dog's tail and leg; tests of renal vein blood from ischemic kidneys.

Patency of the Uterotubal Junction of the Rabbit; Experimental Observations with the aid of CO_2 Insufflation (Rubin Method). M. Feresten and S. Wimpfheimer. Endocrinology, 24: 510, April 1939.

The tonicity of the uterotubal junction was studied in 48 living rabbits by means of the Rubin test.

There was a marked variation in the degree of patency of the uterotubal junction at each stage of the estrous cycle.

The degree of patency of the right and left uterotubal junction was frequently different when insufflated under identical conditions.

Once the ostium between the uterus and tube was opened by the varying gas pressures, a constant fluctuation level of less than 100 mm. Hg. was maintained.

The uterotubal junction of the rabbit appears to be guarded by a sphincter-like apparatus and polypoid projections, which offer a greater resistance to gas passing upward from the uterus than downward toward the uterus.

Massive Dose Arsenotherapy of Syphilis by the Intravenous Drip Method; Five-year Observations. H. T. Hyman, L. Chargin, and W. Leifer. Am. J. Med. Sci. 197: 480, April 1939.

Twenty-five patients, treated in 1933 by the intravenous drip method, received an average dose of 4.0 Gm. neoarsphenamine in less than 5 days, without further therapy. No deaths or serious complications occurred.

Ten cases disappeared from observation too early to be judged satisfactorily. Of the remaining 15 patients, 13 became seronegative. They remained so for a period of 30 months (2 cases), 42 months (1 case), 54 months (10 cases). None showed

evidence of clinical or serologic relapse at any time. Another patient, after a satisfactory course returned at 38 months with a reinfection, and was accepted as such by a dermatologic society. The 15th case had been negative up to 19 months, and returned in his 20th month with a new lesion, but the required criteria for reinfection could not be met.

Of these 15 patients, spinal fluid examinations were made on 13, all of which proved negative; 9 patients also had normal teleoroentgenograms, one at the end of 4 years and the others at the end of 5 years of observation.

A Method of Raising Venous Pressure to be used in Surgical and Traumatic Shock. G. G. Ornstein, S. Licht and M. Herman. Quart. Bull., Sea View Hosp. 4: 333, April 1939.

Following Henderson's suggestion, that in shock the small blood vessels in the muscles and peripheral circulation form a reservoir for the blood of the depleted general circulatory system, the large groups of muscles in the lower extremities and back, were electrically massaged with an interrupted Faradic current.

Venous pressure determinations in 38 young healthy adults was found to rise an average of 3.5 centimeters, and in no case was there a failure to increase the venous pressure. In a few patients with surgical shock, the venous pressure could be increased at will by the same method.

Treatment of Early Measles with Parental Whole Blood. J. L. Kohn, A. E. Fischer and H. V. Ruch. J. Pediat. 14: 502, April 1939.

The etiological agent of measles is a filtrable virus. If given early enough after exposure, serum from immune persons has a neutralizing effect on the virus. Pulmonary complications in measles appear to be due to the presence of pathogenic bacteria. Post mortem cultures of such lungs usually yield hemolytic streptococci. Less frequently pneumococci or influenza bacilli are found. It was hoped that the blood from immunes would also have neutralizing effects on these bacteria. In an attempt to reduce the incidence of pulmonary complications, 66 children under three years of age were injected subcutaneously during the pre-eruptive or early eruptive stages of measles with 20 cc. to 40 cc. of adult blood.

There was very little difference in the severity of measles or in the incidence of pulmonary involvement, when these children were compared with others who did not receive blood injections.

Absorption of Sulfanilamide from Rectum and Colon of Rabbits. L. Nerb, R. Turell and A. W. M. Marino. Brooklyn Hosp. J. 1: 88, April 1939.

Sulfanilamide administered to rabbits by rectum in the form of solution, suppository or capsules is absorbed rapidly. The rabbits were found to be unsatisfactory animals for this experiment because they frequently expelled all or parts of the chemical. In spite of these difficulties, various amounts of sulfanilamide were found in the blood. The concentration of sulfanilamide in the blood stream was found to be the same in two rabbits when equivalent amounts were first administered orally, and in three days rectally. The possibilities that following rectal administration, the drug may be propelled to the ileum and absorbed from there were considered.

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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; "r", a combined radiology and radiotherapy conference report. Author entries are made only for original articles.

NEWS AND NOTES

ANOTHER GOLD MEDAL FOR DR. BELA SCHICK

At the Annual Meeting of the Third Forum for Allergy which took place on January 12, 1941, in Indianapolis, Indiana, in recognition of his outstanding contributions in the field of allergy, Dr. Bela Schick was presented with a gold medal bearing the image of Dr. Clemens Von Pirquet.

In his acceptance speech, Dr. Schick emphasized the fundamental work in the development of the science of immunity done by his friend and teacher, Clemens Von Pirquet.

He expressed the hope that the day is not remote when a Von Pirquet Institute for Research would be founded in this country.

OF INTEREST TO RECENT GRADUATES

Through the kindness of Mrs. Charles Klingenstein, a devoted friend of The Mount Sinai Hospital, a provision has been made whereby graduate internes, and a limited number of members of the Out-Patient Department may be placed on the mailing list of the JOURNAL OF THE MOUNT SINAI HOSPITAL for a period of one year on payment of fifty cents (to cover mailing expenses).

Those who are interested may apply to Dr. Joseph H. Globus, Editor-in-chief of the JOURNAL.

TO OUR SUBSCRIBERS

The JOURNAL OF THE MOUNT SINAI HOSPITAL would appreciate the cooperation of its readers in the matter of the renewal of subscriptions.

The prompt return of the accompanying renewal blank would obviate the need for annoying reminders and time consuming correspondence. Moreover, it would help materially in our efforts to keep the mailing list of the JOURNAL in good order.

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