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Modern Concepts of Drug Reactions*

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In discussing the drug reactions, it is important that we have a clear understanding of the terms used. In a symposium organized by the Council for International Organization of Medical Sciences, held in Liege in 1957, a general classification was adopted which was originally suggested by E. A. Brown in 1955. While this classification is not complete and will probably need further classification, it is ideal for the purposes of this presentation (Table I).

1. OVERDOSAGE

With overdosage of a drug, toxic effects in direct relation to the total amount of the drug in the body may occur. These effects are to be anticipated in any patient provided a threshold blood level is exceeded. Such overdosage may be absolute and may result from an excess given in error or as a result of accumulation of the drug in the body.

Under certain conditions, a relative overdosage may occur: the usual signs and symptoms of excess or of toxicity are produced by a reduced or normal dose of the drug because of an underlying abnormality in the patient. Thus, in the presence of renal failure, drugs which are normally excreted in the urine, may produce a markedly raised blood level and toxic effects. For example, patients with renal tuberculosis associated with renal failure often tolerate only small doses of streptomycin. Similarly, potassium may prove dangerous in uremic patients and hexamenthonium may produce severe and prolonged reactions in these patients.

2. INTOLERANCE

Intolerance to drugs may be defined as a lowered threshold to normal pharmacological activity of a drug. Some patients have symptoms of cinchonism on very small doses of quinine. Intolerance may also result from the extremes of normal biological variation, either in absorption, metabolism, excretion, or susceptibility to the drug.

3. SIDE EFFECTS

The Conference decided that this term should be reserved for therapeutically undesirable but unavoidable effects of drugs. These may be specific or nonspecific, *i.e.*, unknown as yet. Finally, with the plethora of new drugs being in-

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troduced and, unfortunately, too often without sufficient clinical investigation, new side effects may occur for which the clinician is unprepared.

Specific Side Effects

A specific effect means that the undesired effect is a result of the normal pharmacological effect of the drug; so that the dose has to be graduated to produce maximum desired pharmacologic action with the minimal undesired effect. Thus, the hypnotic effect of certain antihistamine drugs may limit their dosage. In other cases, side effects may be produced because the drug acts as a histamine-releasing agent, so that the desired action may be overshadowed by the histamine effects.

A more recent understanding of some of these side effects is that some drugs

TABLE I

Nomenclature

1. Overdosage
   a) absolute immediate
   b) relative cumulative
2. Intolerance
3. Side Effects
   a) specific
   b) non-specific
4. Secondary effects
5. Idiosyncrasy
6. Hypersensitivity—allergic reactions
7. Miscellaneous—Difficult to classify with above
   a) light sensitivity
   b) fixed eruptions
   c) hyperpigmentation and depigmentation
   d) granuloma and others
   e) cystic lesions

may compete in a normal metabolic cycle. Chalmers has pointed out that epileptic patients under treatment with phenytoin and primidone may develop a megaloblastic anemia, because the drugs inhibit the action of folic acid (2).

No drug is usually given deliberately which is known to have a hemolytic effect by direct damage to the cell membrane. Several drugs may affect the globin, an effect which is probably demonstrated by the appearance of the Heinz bodies within the red cells. Of these, the best known are potassium chlorate, promanide, and phenylsemicarbazide.

Potassium chlorate produces a rapid destruction of cells. There are variations in susceptibility, which depend on the balance between the absorption of the salt from the gut and its excretion in the urine, as well as the intrinsic susceptibility of the red cell to damage. In some patients, quite small doses of about ten grams produce acute intravascular hemolysis with consequent anuria, while in others the toxic dose is three or four times as great. Hemolytic anemia which results from the therapeutic use of potassium chlorate is thus a manifestation

of intolerance and occurs only in those at one extreme of the distribution curve of sensitivity.

Promin® (promanide), a sulphone regularly produces a hemolytic anemia, apparently by affecting the cell surface, but possible hemolytic or enzyme systems are involved, since methemoglobin is also formed.

Megaloblastic anemias are now usually attributable to deficiency of vitamin B_{12}, folic acid, or both of these substances. It has been suggested that anticonvulsant therapy, particularly the use of phenytoin and primidone, may interfere with enzyme systems concerned with folic acid metabolism and result in megaloblastic anemia.

Colchicum is an alkaloid found in the plant, Colchicum autumnale; Malkinson and Lynfield described the appearance of alopecia following the administration of the drug in three cases (3). The drug had been used for the treatment of widespread psoriasis. Colchicum is an antimitotic agent similar to the folic acid antagonists. Hair loss in patients following the administration of Colchicum or its derivatives, has been recorded many times in the medical literature. Loss of hair occurs most frequently after relatively large doses of Colchicum, and is usually noted two to three weeks after initial administration of the drug. It may be presumed that Colchicum alopecia is related in some way to the antimitotic action of the drug.

4. SECONDARY EFFECTS

Secondary effects are defined as the indirect consequence of a primary drug action. They are not the pharmacological result of drug administration, but occur because of some additional effect of the drug. For example, the side effects or secondary effects of antibiotics can be cited including the occurrence of moniliasis and specific evidence of vitamin deficiency.

Soon after broad spectrum antibiotic drugs became available for therapy, reports appeared in the literature describing monilial infections of the anogenital area and oral mucosa. Cannon has reported upon the problem of the rising frequency of monilial infections in relation to antibiotic therapy.

Loh and Baker studied the fecal flora of nineteen normal subjects following the administration of broad spectrum antibiotic therapy and found that in most instances there was rapid 100-fold to 1000-fold increase of *Candida albicans* (4). In four patients who had previously shown no yeasts, the presence and proliferation of yeasts was observed during and following medication. The authors concluded that the growth of yeasts seemed to be stimulated by the antibiotics either directly or indirectly through suppression of other organisms.

Kligman observed that *Candida albicans* regularly emerges in abundance in the mouths and gastrointestinal tracts of those receiving wide spectrum antibiotics (5). Keefer, as well as Woods, Manning and Patterson also reported on oral, intestinal, bronchopulmonary, genital, dermal, and generalized monilial infections following the use of antibiotic therapy.

In 1955, Peck *et al.* reported their experiences with serodiagnosis of moniliasis (MCFT) (6). They prepared many antigens and found the best antigen was

from *Candida albicans* isolated from a fatal case of generalized moniliasis. The antigen was stable and could be kept in solution at 6°C for years. The aqueous, heat-treated antigen was the most specific. Alcohol antigens and HCl antigens were discarded as unsuitable.

They could summarize their findings as follows:

1. The incidence of positive reactions with this test in a series of 793 with a variety of unselected dermatoses was 13.5 per cent.

2. The incidence of positive MCF results in a series of 120 sero-positive treated syphilities was 17.5 per cent indicating that this antigen does not contain any Wassermann-reacting lipoidal substances.

TABLE II

Monilia complement fixation technique (MCFT)

Qualitative Test	Test	Control
Overnight at 4°C		
	ml.	*ml.*
Patient's serum	0.1	0.1
Veronal	0.2	0.5
Buffered saline complement	0.3	0.3
3–5% Units* monilia antigen**	0.3	—
37°C water bath—30 minutes		
Sensitized sheep cells	0.6	0.6

* This technique is described by Dr. John F. Kent (The Army Medical Service Graduate School Washington, D.C.) for a serolic test for syphilis.

** The monilia extract is first subjected to an anticomplementary and a hemolytic titration. It is then subjected to an antigen titration to determine the dilution which presents the highest degree of sensitivity with a serum from a patient with known positive moniliasis. Employing this dilution of antigen, a large number of sera from normal patients are tested to evaluate the specificity of the antigen.

3. In a series of 48 patients with clinical moniliasis 36 or 75 per cent gave positive MCF tests.

4. There was no correlation between positive stool cultures and MCF results in a series of 50 patients.

5. In a series of 186 patients with pustular skin diseases, long-term tetracycline therapy did not affect MCF results. Those who were sero-negative prior to therapy remained sero-negative in individuals under therapy for as long as 4½ months.

6. There was no correlation between MCF and the incidence or degree of gastrointestinal complaints such as nausea, vomiting, cramps, diarrhea or flatus.

7. There was a marked correlation between MCF results and the development of anogenital pruritus. Of the 27 sero-positive reactors prior to tetracycline

therapy, 21 (81%) developed anogenital pruritus shortly after institution of therapy.

5. IDIOSYNCRASY

True idiosyncrasy implies an inherent qualitatively abnormal reaction to a drug. The best example is the occurrence of a hemolytic anemia in American Negroes given Primaquine® as an antimalarial.

The results of Dern, his colleagues elucidating the pathogenesis of the hemolytic anemia which occurs after the administration of Primaquine® are of extreme theoretical as well as practical importance (7). This anti-malarial drug is harmless to nearly all Americans of Caucasian origin. Nine American Negroes out of ten can take the drug without any ill effects, but the tenth will develop, in the course of a few days, a moderate hemolytic anemia in which the hemoglobin falls 40 to 50 per cent, the reticulocyte count rises to 2 to 3 per cent, and the excretion of urobilinogen increases. When the drug is withheld, the blood is rapidly restored to normal.

Through experiments in which cells from a susceptible individual were tagged and transfused into a normal subject, and vice versa, prior to challenge with the drug, it was found that the susceptibility occurred only in those cells of the susceptible individual aged more than 50 to 60 days, these aged cells were destroyed because Primaquine® inhibits an enzyme, glucose 6—phosphate dehydrogenase, which is needed to maintain cell integrity. This enzyme is present in demonstrable, but reduced amount in the red cells of susceptible individuals. Not only is it reduced in quantity, but it is also more readily inactivated by heat than in normal subjects. It seems almost certain that Primaquine® sensitivity is one manifestation of an inherited abnormality of red cell enzyme systems: there is as yet no proof that this sensitivity is genetically determined though this appears likely.

In addition to its enzyme inhibiting action, Primaquine® produces Heinz bodies in sensitive cells, and, therefore, presumably denatures globin. Cells sensitive to Primaquine® are sensitive also to sulphanilamide and acetanilid, and less regularly, to sulphathiazole, phenylhydrazine, sulphoxone sodium (Diasone®) and phenacetin. These observations shed some light on the very rare hemolytic response to sulphonamides. Perhaps many other drug-induced hemolytic processes will prove to be due to inhibition of enzymes. Beutler has shown that in the erythrocytes of Primaquine®-sensitive subjects, reduced glutathione is more readily oxidized than in the erythrocytes of normal subjects. Sansone and Segni (8) claim that this occurs also in favism, and Szeinberg (9) and his associates have shown that in Israel favism and drug-induced hemolytic anemia are associated with low levels of glutathione in the erythrocytes. This subnormal level of glutathione in the erythrocytes is a familial trait which appears to be a Mendelian dominant. The gene causing this character difference is very rare among Ashkenazi Jews, but common among Sephardic Jews; its presence is often discovered when an immigrant to Israel from the oriental diaspora returns, to eat fava beans for the first time in his life.

It is now possible to test cells *in vitro* for abnormal sensitivity to Primaquine® because under the conditions specified by Beutler, Dern and Alving (10, 11) acetylphenylhydrazine produces more than five Heinz bodies in less than 30 per cent of cells from a normal subject, whereas this effect is produced in more than 45 per cent misclassification of normals. One may hope, therefore, to be able to identify those patients who have been born with an abnormal set of enzymes.

6. HYPERSENSITIVITY-ALLERGIC REACTIONS

The term hypersensitivity, is differentiated from idiosyncrasy because in hypersensitivity drug reactions, the clinical symptoms are conditioned by previous exposure to sensitization by the drug, involving a mechanism conditioned or mediated by an antigen-antibody reaction. The etiology of many commonly seen drug-eruptions has, as yet, certainly not been explained on this antigen-antibody reaction. At best, such a mechanism has been assumed. In a number of the urticarial type of eruptions, an antigen-antibody mechanism has been well demonstrated. In others, which clinically cannot be differentiated, the Prausnitz-Kustner reaction has been negative. This finding has been explained by the supposition that the antigen for eliciting the positive reaction was not the one actually used.

In other words, the drug so modified to form a complex *i.e.* the final heptane, was certainly not used in eliciting the reaction. The mechanisms of drug eruptions which resemble the exanthemata, as well as the eruptions due to bromides and iodides have not as yet been explained.

Blood Dyscrasias

The blood dyscrasias properly belong under the true sensitivity reactions. The concept of enzyme inhibition is comparatively recent. However, it has been shown that a drug may combine with the protein of the recipient to form an antigen foreign to the host. Landsteiner's study of artificial antigens made by coupling aromatic amines with proteins and with their capacity to cause skin sensitivity is well known.

It is accepted by many research workers that a good number of drugs act as pro-antigen or pro-protein. Zozaya demonstrated that antigenic activity could even be conferred on a crystalloid by absorption onto a nonprotein macromolecular carrier tightly enough to induce antigenic activity. Drug after drug has been shown to be more or less tightly absorbed onto serum albumin; *viz* the sulphone amides, antibiotics, and dyes, such as Evans Blue. While these evidences may be taken as the primary bases for incriminating a drug as a haptene, true hemolytic anemia resulting from such mechanism has been substantiated rarely.

Harris reported a patient who developed a hemolytic anemia while receiving the antimony-containing drug, stibophen (Fouadin®) (13). This patient's serum contained a factor which, in the presence of added stibophen: a) agglutinated the patient's red blood cells, b) agglutinated the red blood cells of normal sub-

jects, c) sensitized normal red blood cells to the antiglobin agent, d) hemolyzed, trypsinized normal red blood cells, and, e) hemolyzed the red blood cells of the patient with paroxysmal nocturnal hemoglobinemia. The patient's serum in the absence of added stibophen was inert and could be transfused into a normal recipient without incident, but when the recipient received a dose of stibophen, his own cells were hemolyzed. In this case, the specificity of the reaction was shown to depend on a comparatively simple component of the stibophen molecule, *i.e.* the patient's serum could be activated not only by stibophen, but also by sodium catechol disulphonate, an essential part of the stibophen molecule.

Another interesting observation was that of Freedman, Barr, and Brody, who recorded a case of hemolytic anemia due to quinidine (14). The patient's serum contained an agglutinin, which reacted with any red cell in the presence of quinidine, in concentration comparable to that attained in treatment and lysed them in the presence of human or guinea pig complement. The optical isomer of quinidine, quinine, was completely ineffective in linking antibody to cell.

THROMBOCYTOPENIC PURPURA DUE TO DRUG HYPERSENSITIVITY

The underlying mechanism in cases of thrombocytopenia due to any of a large number of different drugs, has been shown to be abnormal serum factor, an antibody which destroys platelets only in the presence of the drug. A similar mechanism has been observed in the case of hemolytic anemia due to stibophen previously reported by Harris (12).

Ackroyd (11) states that the clinical picture in drug-induced thrombocytopenic purpura is indistinguishable from that of the idiopathic variety. He suggests that the diagnosis can be established only by administration of small doses of the drug to provoke a mild attack. He also maintains that patch testing sometimes gives a positive result. In a case of thrombocytopenic purpura due to Sedormid®, Mescher demonstrated precipitate formation and a reduction in clot reaction by the drug, but was unable to demonstrate platelet agglutination using sedimentation methods (15). However, in three cases of sedormid purpura, positive patch tests were obtained. In the patch testing with Sedormid®, a suspension of sedormid crystals in a saturated solution of Sedormid® in prophylene glycol, is applied to the skin in patients who have recovered from Sedormid® purpura. There is no wheal formation to suggest histamine release and no gross evidence of inflammation. The lesion does not blanch. All that is formed is a purpuric reaction. The platelet count remains unchanged. It should be realized that the period during which the antibody remains detectable in the patient's blood is extremely variable.

SERUM SICKNESS TYPE OF REACTION

Over twenty years ago Sobotka, Kahn and Peck (16), studied the production of serum sickness-like reactions with 5,5-phenylethylhydantoin (Nirvanol®), a drug used in the treatment of epilepsy. This type of reaction could not be elicited in animals although its incidence was ninety per cent in patients treated with the drug. Synthetic dextrophenylethylhydantoin, though slightly less effective

than racemic phenylethylhydantoin (Nirvanol®) was about one-third as toxic, emphasizing the importance of chemical asymmetry on physiologic effects. The drug reaction caused by the levoform of phenylethylhydantoin was presumed to result from its function as a spontaneous haptene.

PENICILLIN ALLERGY

The reactions to penicillin take two distinct forms: one is the serum sickness type, the other is the vesicular type, usually localized on the hands and feet, resembling the trichophytids and bacterids. When this reaction was first noted, Peck and Siegal carried out a number of experiments which demonstrated its etiologic mechanism (17). Amorphous and crystalline penicillin, as well as streptomycin, were used as antigens in animal experiments. Throughout the work, a Dale test using the uterine horn as test object was employed to demonstrate anaphylaxis. Cross sensitization was determined between these two antibiotics and also between them and trichophytin. Other experiments were also performed to demonstrate local anaphylaxis (Arthus) and to elicit the Schwarzman phenomenon.

Guinea pig anaphylaxis to amorphous penicillin was first demonstrated by McCloskey and Smith (18), but it should be noted that sensitization of the guinea pig to penicillin is limited by the toxicity of this antibiotic for the species. Furthermore, Chu and Cutting have reported negative results with crystalline penicillin in experiments on guinea pigs (19). They were unable to demonstrate positive Dale reactions or any response with other isolated organs. Peck and Siegal showed irregular anaphylactic sensitization with crystalline penicillin; a positive Dale reaction was obtained on one horn only in four of nine animals. A Schwarzman phenomenon was not obtained with penicillin. Trichophytin, another product of fungi, also could not be used either as an eliciting or a preparatory factor in the Schwarzman phenomenon (20). In view of these findings, it is hazardous to ascribe a causative relationship between penicillin and any hemorrhagic phenomenon observed following administration of penicillin or perhaps any of the other antibiotics.

In a recent meeting held in London there still was a discussion of cross-sensitivity reactions among penicillin and trichophytin. The work which we have done, both clinically and experimentally, seems either to have been overlooked or misinterpreted. In our guinea pigs injected with amorphous penicillin, there was not a single positive Dale reaction to trichophytin or penicillin in the guinea pig in the course of T. gypsum skin infection.

We tested 406 adults and 101 children with penicillin, amorphous, and crystalline, and with trichophytin; 110 patients were also tested with streptomycin (21). For the penicillin skin test we used an intradermal injection of 0.1 cc of saline containing 2,000 units of crystalline penicillin G. For the streptomycin test, we employed 500 units in the same volume of diluent. Higher concentrations of either antibiotic were found to give some non-specific irritative reactions. The test was read in 48 hours, as with trichophytin or tuberculin reactions. A positive reaction to crystalline penicillin consisted of an area of definite

erythema more than one cc in diameter, usually accompanied by a definite edema and infiltration, and often studded with vesicles and papules. Skin tests with streptomycin are difficult to evaluate because of the non-specific inflammatory reactions produced, *i.e.*, when 500 units are used.

Interpretation of positive penicillin skin tests in patients who have never received penicillin is as follows: positive penicillin were found in skin tests in 15 of the 276 adult patients who had never received penicillin and among 17 of 130 who had received such therapy. As had been shown by Peck and Hewitt (22), this is not a non-specific reaction. It has been demonstrated that the common causative organism of dermatophytosis, T. gypseum, is capable of producing an antigen in Sabouraud's bouillon, which could be identified as penicillin G. Therefore, these so-called spontaneous reactions to penicillin actually demonstrate an acquired penicillin sensitivity in patients who have had previous fungus infections. Thus, the conclusion appears justified that the dermatophytes sensitize the skin to a penicillin-like substance, just as they do to trichophytin. Penicillin sensitivity thus induced is independent of trichophytin sensitivity. They are often associated because of a common origin. It is not true, as some authors have claimed, that they are a common antigen. That there is no common antigen between crystalline penicillin and trichophytin, is based on the following considerations:

Crystalline penicillin G presumably contains nothing but crystals of pure penicillin. When an aqueous solution is heated, its antibiotic potential is destroyed. If the preparation is then neutralized to its previous pH, and used for testing in a patient whose skin is reactive to untreated crystalline penicillin, a negative test is obtained. Thus, the antigen must be identical with penicillin itself.

In contrast with penicillin, trichophytin is much more stable, is heat resistant and it resists the action of hydrochloric acid.

As a further evidence for the distinct separation of the common trichophytin antigen from penicillin, the following experiment was carried out. A strain of T. gypseum furnished by Lewis was inoculated into penicillin media, and it was shown to be capable of producing small amounts of a penicillin-like factor. Trichophytin was then made using the same organism grown in routine fashion in Sabouraud's bouillon. This trichophytin was shown to have no antibiotic activity. It gave a positive reaction in the trichophytin-sensitive patient which differed in no way from the reaction obtained from the same trichophytin, to which no hydrochloric acid had been added. In another patient sensitive to crystalline penicillin sodium G, intradermal tests with the trichophytin preparation both treated and untreated with hydrochloric acid, were negative; this experiment showed that an active trichophytin antigen made from a strain of fungus capable of producing a penicillin-like factor, was completely distinct as an antigen for penicillin itself.

Although often associated, clinical observations show that penicillin allergy and trichophytin allergy are distinct. In our series among 15 patients with spon-

taneous latent penicillin sensitivity, 6 were negative to trichophytin. Penicillin sensitivity can exist in the absence of trichophytin sensitivity.

Finally, we were able to sensitize a patient to penicillin and then desensitize the same patient with increasing doses of penicillin. This, did not alter the trichophytin reaction, which was simultaneously present.

Among 130 patients receiving penicillin treatment whom we tested with penicillin and trichophytin, the incidence of trichophytin sensitivity was not greater, but actually less, than among those not receiving penicillin. More importantly, in human beings who have induced penicillin allergy of the urticarial serum sickness type it is not associated with a high, but rather low, incidence of trichophytin sensitivity, even though a positive 48 hour penicillin skin test is induced.

I believe that we have shown enough data to conclude that the antigens of trichophytin are distinct from crystalline penicillin and that there is strong evidence against the existence of any common antigen between them. Our experiments in guinea pigs' anaphylaxis did not yield any evidence of any cross-sensitization between these two substances.

CONTACT DERMATITIS DUE TO DRUGS

Contact dermatitis in this presentation is defined as the inflammatory changes produced in the skin and its appendages by externally encountered irritants. Nearly all contact dermatitis may be attributed to chemical agents. These may be either *primary irritants* or *sensitizers.*

The dermatitis due to the sensitizers will be referred to as allergic contact dermatitis. The term "eczema" will be avoided, although the mechanism producing both of these conditions is the same in many instances. While in the larger context of the term contact dermatitis, physical agents such as trauma, heat and cold, as well as radiant energy could be accepted as etiologic agents, changes due to them will not be discussed in this presentation.

Primary Irritants: A primary irritant is an agent *which will cause dermatitis by direct action on the normal skin* at the site of contact if it is permitted to act in sufficient intensity or quantity for a sufficient length of time.

The primary irritants can be further subdivided into three main groups. This classification has been useful to me in diagnosis, prevention and treatment.

Sensitizers: A cutaneous sensitizer is an agent which does not necessarily cause demonstrable cutaneous changes on first contact, but which may *effect such specific changes and so sensitize the skin that,* after five to seven days or more, *further contact* on the same or other parts of the body *will cause dermatitis.*

The sensitizers cause the true "*allergic contact dermatitis,*" a term often used synonymously with "*allergic contact eczema*" or just "contact eczema."

Cross-Sensitization as a Factor in Recurrent Reactions of Allergic Origin

We are often confronted with the problem of the recurrent reaction after we have believed that the proved etiologic agent was removed from the patient's environment.

When the reaction is due to a *primary irritant* and the injury is such that permanent effects are not expected, ordinary healing takes place quite readily in most instances. There is no problem of persistence due to a *sensitizer*, even if it is apparently quite severe; once the initiating allergen has been removed, recovery is rapid and progressive.

When confronted with a reaction due to a known sensitizing chemical which has been removed, apparently from the patient's environment, and the reaction still persists, we have been forced to fall back on one of the following explanations: 1) a non-specific sensitization, or 2) a new and unknown sensitization. In many of these cases, we may be dealing with cross-sensitization which is unrecognized.

Many instances of so-called polyvalent sensitivity are due to the fact that the sensitizing agent, from an immunochemical point of view, is unknown and therefore these cases, which are assumed to be due to sensitization to polyvalent unrelated chemicals, are actually examples of cross-sensitization.

It is important, therefore, that we recognize and acquaint ourselves with the chemical structure of the sensitizer in order to prevent recurrences or persistence of the dermatitis in many of these puzzling cases of allergic contact dermatitis.

The Patch Test

For most dermatologic allergies, especially in contact dermatitis, there is nothing which has proved its value as a diagnostic aid as well as the *patch tests properly carried out.* We believe that this statement is accepted by nearly everyone.

7. MISCELLANEOUS REACTIONS

Lichen planus-like

There are the eruptions of a rather puzzling nature, which were found during World War II to be due to Atabrine®. These were lichen planus-like eruptions, atrophies, hypertrophies, and pigmentary changes, especially of the nails. Similar types of eruptions are seen because of Atabrine® and closely allied drugs which have become widely used as a treatment for discoid lupus erythematosus.

Induced Light Sensitivity

Chlorthiazide and hydrochlorthiazide are two compounds that are aromatic sulphonamides, differing from each other only in that in the hydrochlorthiazide, the 34 carbon nitrogen bond is saturated by two hydrogen atoms, whereas in the chlorthiazide molecule it remains dehydrogenated.

Harber, Lashinsky, and Baer reported four patients with eruptions similar to lichen planus and sunburn lesions associated with photo-sensitivity due to chlorthiazide and hydrochlorthiazide (23). The action spectrum in photosensitization due to these drugs were shown to be the wave length range between 2750A and 3100A, *i.e.*, in the sunburn part of the ultraviolet spectrum. The

available evidence suggests that the photo-sensitizing action of these drugs is based on a photo-allergic, rather than a photo-toxic mechanism. Since the patch tests were negative even negative demonstration of a photo-toxic reaction in patch tests, followed by adequate sun and carbon arc lamp exposure, it seems to indicate the possibility that, when the drug is metabolized after ingestion, a photo-toxic compound results that is not formed on the skin after topical application or in the skin after intracutaneous injection.

On the other hand, Cahn and Levy studied fifteen persons in an attempt to determine what specific light factor may be the cause of the dermatitis in patients receiving chlorpromazine (24). Reactions of photo-sensitivity to chlorpromazine developed only on exposure to intense summer sunlight, containing ultraviolet light lengths of between approximately 3025A and 2968A. The patients in this group did not react to hot quartz ultraviolet light, which lacks the spectrum just mentioned.

A different sort of mechanism is demonstrated when a substance capable of absorbing light is added to a biologic system, the system may become so sensitized as to initiate a photo-chemical reaction. For example, sunlight has no effect on red blood cells suspended in saline and exposed to sunlight of wave lengths over 3200A. But, if a small amount of eosine or other fluorescent dye is added, hemolysis occurs. The dye sensitizes the system to light. This is referred to as a photo-dynamic action.

Many substances may produce photo-sensitivity of the skin. When applied to the skin, coal tars, dyes, sulphonamides, and some derivatives of paraminobenzoic acid may produce photo-sensitivity. Administered parenterally, porphyrins, dyes, certain barbiturates, chlorpromazine and sulphonamides may sensitize the skin to light. A distinction between primary photo-sensitivity and allergic photo-sensitivity must be made. All persons given an intracutaneous injection of sulphanilamide, followed by irradiation in the sunburned spectrum at the site will show a local erythematous reaction, followed by pigmentation. However, in some individuals an inflammatory reaction will appear at the same site ten days after the test, and each subsequent exposure of the sensitized persons to ultraviolet light will reproduce the inflammatory response within 24 hours.

Fixed Eruptions

These are lesions that appear at given sites after drug exposure. Most, if not all, are manifested after ingestion and they will reappear at the same sites on subsequent readministration. The appearance of the lesions may vary. Most often they are seen as circumscribed eczematous patches with erythema and pigmentation. They are usually found on the skin, but mucous membrane especially of the mouth are not infrequently involved. Characteristic of the phenolphthalein eruption are lesions in the mouth (tongue) and on the penis. Fixed eruptions may also be urticarial, erythematous, vesicular or bullous and they may even ulcerate.

It should be noted that a given type of eruption is usually elicited by the

same drug and usually appears at the same site. Some authors have reported cross-reactions of drugs of an entirely different structure. The mechanism of such a reaction is obscure. I have had a patient who exhibited several patches of a fixed eruption to phenolphthalein who on a larger dose than usual of the drug developed a generalized eruption. This was first seen as an increase of new patches. As the drug was administered again in larger doses there finally developed a generalized maculopapular eruption with vesicular changes in some of the lesions.

It has been suggested that the antibodies are fixed in the skin where the eruption appears. To study this point several observers have attempted full thickness grafts of previous sites of fixed eruptions into areas of normal skin and then attempted to re-elicit the eruption in the graft. The results of these experiments were contradictory. The work of Wise and Sulzberger which has been repeated by others could not support the view that the epidermis was the site of the shock tissue (25).

The most frequent drugs to induce fixed eruptions are barbiturates and phenolphthalein. Ashton L. Welsh in a recent book (1961) has compiled a list of about 200 drugs that have been reported to produce fixed eruptions (26). These seem to run the gamut of most of the commonly used medications including some foods.

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Digitalis and Dehydration in the Control of Angina Pectoris

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The vast array of drugs and methods used in the treatment of angina pectoris attests to the failure of wide applicability of any one of them. The search continues for other modalities which might prove effectual in the relief of the anginal syndrome. The present study was undertaken to define the limits of usefulness of the method of dehydration and digitalization in this syndrome.

MATERIAL

All the clinical material was derived from one office devoted to the care of patients with cardiac diseases. Those patients with angina pectoris who satisfied the following criteria were included in the study:

1. Previous records were available; details of their past clinical course served for comparative analysis. The reliability of the patients for investigational purposes could thus be estimated.
2. A stable pattern of anginal pain. In most instances, stability was present for over six months. Excluded were those with a recent change in the pattern of angina pectoris, evidenced either by increased frequency and/or intensity of pain, or by the recent development of nocturnal pain.
3. Stability of serial electrocardiograms and the presence of a normal rate of erythrocyte sedimentation. Instability of either the pain pattern, the electrocardiogram or the sedimentation rate might evidence myocardial necrosis, following which anginal pain often alters or remits entirely.
4. Absence of significant clinical signs of congestive heart failure. Patients made no complaint of dyspnea on effort. Neither pulmonary congestion, hepatic engorgement nor peripheral edema was clinically in evidence.
5. Treatment with either digitalis or diuretics had not been previously instituted.

METHOD

Twenty-eight patients were used in this study. Routine examination included determination of the weight, fluoroscopic estimation of the cardiac size, electrocardiogram, hemoglobin, determination of the arm-to-tongue circulation time by the intravenous sodium dehydrocholate (Decholin) method, and, in most patients, the erythrocyte sedimentation rate. Meralluride (Mercuhydrin®) was then given intramuscularly in a dose of 2 cc. On this same day Digoxin 1.25 mg was given orally in divided doses. Beginning the following day the patients were instructed to take acetazolamide, (Diamox®), 250 mg each morning,

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Digoxin 0.25 mg twice daily, and to adhere to a diet restricted in salt intake. Two weeks later the patients were re-examined and all studies were repeated.

ANALYSIS OF DATA

a). In the group of 28, there were 24 males and 4 females, a sex ratio of 6:1.

b). The average age was 63 years; for males 63.5 years, for females 59.8 years.

c). Hypertension (readings greater than 160 systolic and 90 diastolic) was present in 15 patients: 12 males, 3 females. For the entire group, hypertension had been present for an average of 8.5 years; in the males, 6.6 years, and in the females, 16.3 years.

d). There were 2 diabetics in this group, both males.

e). In 13 of the 28 patients, previous coronary thrombosis had been sustained one to twenty years prior to present study.

f). Total duration of angina pectoris averaged 63.1 months,—range 2 to 180 months; from 2 to 10 months in 7 patients; from 11 to 72 months in 8 patients; and from 72 to 180 months in 13 patients.

g). Duration of a stable pattern of angina pectoris averaged 34.1 months, 2 to 10 months in 14 patients; 11 to 72 months in 8 patients; and 73 to 144 months in 6 patients.

h). Borderline clinical evidences of signs of congestive heart failure were found in only a few of the group: basal pulmonary rales were detected in 4 patients; hepatic enlargement in 2 patients: and minimal peripheral edema in 6 patients.

i). Regular sinus rhythm was present in all 28 patients.

j). Cardiac size: 1). The size of the left ventricle (graded on a scale from normal to 4 plus) showed some degree of left ventricular enlargement in all; grade I enlargement in 5 patients; grade II enlargement in 16 patients; grade III enlargement in 6 patients; and grade IV enlargement in 1 patient. 2). The size of the left atrium evaluated by esophageal barium contrast, was unenlarged in 8 patients; grade I enlargement was found in 14 patients; grade II enlargement in 4 patients; grade III enlargement in 2 patients; and grade IV enlargement in none.

k). Circulation time, arm-to-tongue, by the intravenous sodium dehydrocholate method, (normal 12–13 seconds), showed an average reading of 19.0 seconds, range 10.5 to 30.0 seconds. When the circulation time was correlated with the size of the left atrium the average reading was:—16.4 seconds for left atrium, grade 0: 17.2 seconds for left atrium, grade I; 28.4 seconds for left atrium, grade II and 23.5 seconds for left atrium, grade III.

l). The electrocardiogram showed 1) a normal pattern in 7; 2) a pattern of coronary insufficiency with depression of the RST segments in 1; 3) myocardial fibrosis in 7; 4) classical healed myocardial infarction in 7; 5) a pattern of bundle branch block in 5; and 6) bundle branch block plus coronary insufficiency in one.

m). The erythrocyte sedimentation rate, (Westergren method, normal up to

20 mm per hour) was recorded in only 18 of the 28 patients, in 15 of whom it was normal; in 3 patients minimal prolongation was present, (20 to 30 mm per hour).

Re-evaluation after a two weeks' period of dehydration, digitalization and salt restriction showed the following results:

a) In 23 patients weight loss occurred, ranging from 1 to 8 pounds. One patient gained one pound.

b) Cardiac size as estimated on fluoroscopy was altered in only 2 patients, both the left ventricle and left atrium being reduced one grade in both patients.

c) The circulation time was altered in 25 patients, decreasing in 17, range 0.5 to 8.5 seconds and increasing in 8 patients, range 0.5 to 4.5 seconds.

d) The borderline objective evidences of congestive heart failure cleared in 6 of 7 cases.

e) The electrocardiogram showed a digitalis effect in only 13 of the 28 patients (46%).

f) Sedimentation rates which had been slightly elevated in 3 patients returned to normal values in 2 patients.

RESULTS

In evaluating the results of therapy in a symptom-complex such as angina pectoris, reliance must be placed on the patients' estimation of changes in the character of the anginal pain. As most of the patients complained of chest pain on effort, usually the act of walking, and to a lesser degree, chest pain at rest, chiefly at night, patients were classified as improved if they reported 1) a significant increase in the capacity for walking or other effort, 2) a significant quantitative reduction in the use of nitroglycerine, or 3) a marked decrease or total remission of nocturnal attacks of angina.

a). There was no change in the anginal pain pattern in 14 patients (50%).

b). The pain syndrome worsened in 2 patients.

c). Pain was improved in 12 patients (43%), all males. Four patients showing the greatest weight loss—8, 8, 7 and 6 pounds respectively, were in the category of improvement, suggesting a possible relationship between improvement and loss of latent edema.

d). Correlation of improvement with the initial level of circulation time is suggested by comparing the average circulation time of 21.8 seconds in the 12 improved cases, to an average circulation time of 17 seconds in the 16 unimproved cases. In all three instances where the circulation time was decreased by six or more seconds improvement was reported.

e). Correlation with hypertension. Six of the 12 improved cases were in the hypertensive group, displaying blood pressure readings greater than 160 systolic.

f). Correlation with previous myocardial infarction. Seven of the 12 cases (58%) of improvement had suffered previous myocardial infarction. (For the entire group of 28, previous myocardial infarction was experienced in 13 (46%).)

g). Correlation with cardiac size.

Left ventricle—grade I—1 patient improved, 4 patients unimproved; grade II—8 patients improved, 8 patients unimproved; grade III—2 patients improved, 4 patients unimproved; grade IV—one patient improved.

Left atrium—grade 0—2 patients improved, 6 patients unimproved; grade I—6 improved, 8 unimproved; grade II—2 improved, 2 unimproved; grade III—2 patients, both improved.

DISCUSSION

All 28 patients included in this study exhibited regular sinus rhythm; there was none with auricular fibrillation, a mechanism not particularly common at any stage of coronary disease, but when present, more likely to be found in the very late stages of advanced coronary disease associated with much cardiac enlargement and often overt congestive heart failure. Usually in such patients digitalis and diuretics have already been employed, and often dyspnea due to myocardial insufficiency replaces the painful anginal syndrome due to coronary arterial insufficiency.

The critical factor of latent edema is inherent in the observation that favorable results by this therapeutic method are found predominantly in:

1. patients with the largest left atria.
2. those with the highest initial circulation times.
3. those in whom the greatest reduction in circulation time is effected by this treatment.
4. those showing the greatest weight loss after therapy.

Patients exhibiting these factors are found chiefly in the group with a) established hypertension, b) previous coronary thrombosis, and c) significant cardiac enlargement, all of which tend, in time, toward a state of fluid retention.

While digitalis and diuretics have been previously employed in the control of certain phases of the anginal syndrome, there are no studies directly aimed at assessing the relative roles of the various factors affecting salt and water retention. This study seeks to amplify and to make more quantitative earlier reports on the efficacy of this therapeutic method. Soloff found remarkable relief of nocturnal anginal pain both in patients without, as well as with, objective evidences of congestive heart failure following diuresis with mercurials and the use of a low sodium diet (1). Paul observed favorable results from the use of a mercurial diuretic combined with theophylline in certain patients with angina pectoris refractory to other methods of therapy (2). He believed that this treatment led to increased cardiac output with improvement of coronary blood flow and consequent diminution of pain. Watson reported amelioration in angina decubitus, with frequent nocturnal pain, following the use of low salt diet, and postulated that salt and water retention leading to subclinical congestive failure might underlie the clinical syndrome (3). Rubin and Frieden found that a mercurial diuretic injection was followed by improvement in angina pectoris, with subsequent decrease in the frequency and intensity of anginal pain as well as improvement in exercise tolerance (4). In one patient, acetazolamide, and in two patients, digitalis, were also found effective in this respect.

The loss of significant weight in most of the patients showing distinct relief of anginal pain by the method outlined confirms the impression of the presence of a state of subclinical congestive failure. Significant amounts of extracellular fluid may be present before gross objective signs of fluid retention are apparent. Walser and Griffith have demonstrated that patients in mild heart failure may develop an increase of 5 liters in extracellular water without showing palpable edema (5).

SUMMARY

A method of treating certain patients with angina pectoris who are not in a clinical state of congestive heart failure is described. Dehydration with oral and injectable diuretics together with digitalization is effective in some patients with a persistent and stable pattern of angina pectoris. This group often exhibits long-standing hypertension, very frequently displays significant cardiac enlargement, notably of the left atrium, as well as prolongation of the arm-to-tongue circulation time, and many of these patients have sustained previous myocardial infarction. It is postulated that improvement in myocardial function follows the correction of a state of subclinical congestive failure as evidenced by loss of weight and reduction in the circulation time following the treatment outlined.

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The Mechanism of Shock in Myocardial Infarction*†

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Despite the large number of patients succumbing to myocardial infarction with shock, the precise alterations occurring in this syndrome have not been indisputably defined. This is because there is a paucity of hemodynamic data in humans and it is difficult to produce experimentally.

Investigators have not always applied uniform criteria to the definition of "shock" following myocardial infarction, which adds to the difficulty of evaluating hemodynamic changes and their apparent response to treatment. Generally accepted diagnostic criteria include hypotension with systolic arterial pressure of 80 mm Hg or less in previously normotensive individuals and perhaps 100 or less in previously hypertensive individuals, persisting for at least one-half hour and accompanied by the clinical signs associated with other forms of shock, such as cold skin and alterations in the sensorium. For purposes of standardization, excluded from this category are patients with transient hypotension, generally of mild degree, following myocardial infarction who do not demonstrate circulatory inadequacy, as well as those whose hypotension or shocklike state is attributable to an arrhythmia. The arterial pressure criteria are entirely arbitrary and there have been patients in clinical shock with arterial pressure above this range, but the outlined criteria will include the majority of those with myocardial infarction with shock.

STUDIES IN HUMAN SUBJECTS

Table I lists the cases of myocardial infarction with shock in humans studied hemodynamically in most detail. These data have been compiled by Agress and his associates (1) from the work of several groups (2–5). It is evident that there are significant reductions of cardiac output in cardiogenic shock. Is reduction in cardiac output wholly responsible for the resultant hypotension? Opinions have varied considerably concerning this, ranging from those of Boyer (6) who believes that the shock is entirely attributable to myocardial factors to those of Agress (7) who maintains that there are important peripheral vascular factors in the genesis of the shock syndrome.

In several of the patients with shock there is failure of peripheral vascular resistance to rise sufficiently to maintain arterial pressure as it may in other conditions where the cardiac output is lowered. In others, even moderate rises in peripheral vascular resistance fail to cause maintenance of arterial pressure.

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Although cardiac output is almost uniformly depressed in myocardial infarction with shock, in many instances to levels lower than those in patients without shock, this difference between the two groups is not uniformly evident. Figure 1, from the work of Smith (3), demonstrates that there may be some overlap in cardiac output between the group with and that without shock, although generally the output is lower in the "shock" group. In three of the ten patients with myocardial infarction without shock, the cardiac index was in the range of the "shock" group, but these patients presented none of the manifestations of shock. This must be taken as evidence that the cardiac output may diminish consider-

TABLE I

Hemodynamic alterations in 14 human subjects with acute myocardial infarction with shock

These have been compiled by Agress and Binder (1) from the investigations of 4 groups (2-5). (From American Heart Journal 54: 458, 1957. Reprinted by permission of C. V. Mosby Co.)

Mean Arterial Pressure (mm Hg)	Cardiac index (L/M2/min)	Total peripheral resistance (dynes sec cm^{-5})	Venous pressure (mm H2O)
72	2.4	1300	115
83	1.5	2450	90
73	1.5	2100	140
88	1.6	2350	—
58	1.9	1280	91
54	1.3	1360	176
60	1.4	2080	74
84	1.5	2480	81
70	1.3	2160	149
52	1.6	3900	270
54	0.8	3400	65
25	0.6	1600	175
90	—	1432	—
85	—	2367	—

ably and still not cause shock and suggests that other factors may contribute to this syndrome.

The available evidence indicates that the shock, in many patients, is not explainable solely by severe congestive heart failure. Although the syndromes of shock and congestive failure may frequently coexist and there is obviously severe depression of myocardial function, the patient often presents solely the clinical appearance of shock and no symptoms or signs of congestive failure. According to some the combination of shock and heart failure following myocardial infarction is less common than the appearance of either alone (8). Measurements of venous pressure show considerable differences among the patients with shock, with many within the normal range and others showing relatively moderate elevations. Smith's investigations (Fig. 2) have shown that in many instances the venous pressure is no higher in the group with shock than in that without shock. Similarly, blood volume and central blood volume have

almost universally been found normal (2–5). A disparity, in some patients, between normal blood volume and a rise in venous pressure has suggested that venoconstriction may sometimes be present. It should be realized, however, that it is possible that the blood volume may rise later in the course of acute myocardial infarction with shock, although this has not been definitely established in human subjects. The limited data available indicate that no change in blood volume occurred in a study undertaken four weeks after the initial study (4). However, it is possible that left atrial pressure may be elevated in the presence of normal peripheral venous pressure. There are no data concerning this par-

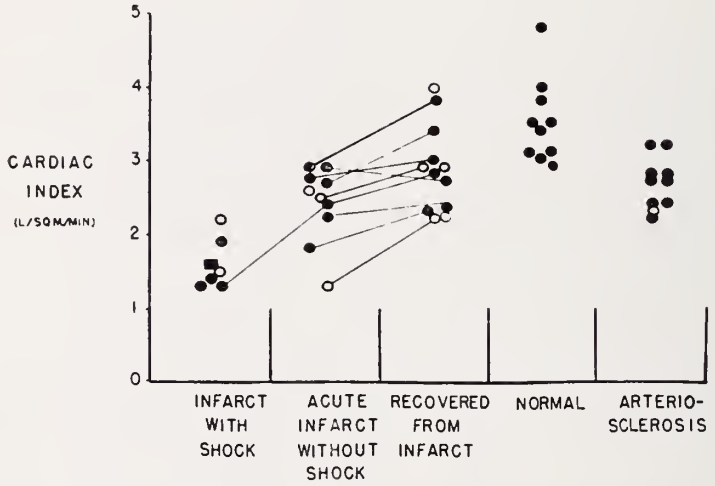

Fig. 1. Alterations in cardiac output in human subjects with acute myocardial infarction with and without shock. Although the cardiac output is generally lower in the group with shock, there is some overlap between the two groups and in 3 of the 10 patients with myocardial infarction without shock, the cardiac index was in the range of the group with shock. (From Smith, W. W. *et al.*, Circulation 9: 352, 1954. Reprinted by permission of The American Heart Association, Inc.)

ticular parameter in humans with acute myocardial infarction but this has been established experimentally in dogs by one group (9).

EXPERIMENTAL STUDIES

Experimental investigation of myocardial infarction with shock has been hampered by the difficulty in producing this syndrome in the experimental animal. It has generally, though not invariably, been observed that ligation of a dog's coronary artery is not followed by the sustained hypotension characteristic of human myocardial infarction with shock (10, 11). Although several technics have been attempted, perhaps the most satisfactory is that of Agress in which plastic microspheres are injected into the ascending aorta of closed-chest dogs (12). Even with this technic, production of shock is inconstant, but enough animals with sustained hypotension, histologic myocardial damage, lowered cardiac output, increase in SGO-T and other enzymes have been studied to form some idea of the significant hemodynamic alterations (12–14).

Figure 3, from our own experiments, indicates the fall in aortic pressure and cardiac output occurring following coronary embolization in the dog. Normal right atrial and left ventricular end diastolic pressures are maintained throughout the four hour duration of the experiments. Although the cardiac output diminishes considerably, the peripheral vascular resistance fails to change appreciably. Accompanying the marked fall in aortic pressure is, as might be expected, a parallel diminution in coronary flow. Figure 4, from the work of Agress (1), shows similar results in dogs with coronary shock, whereas in animals which do not develop shock, there are equal reductions in cardiac output (Fig. 5). In this group without shock, however, the peripheral vascular resistance shows a

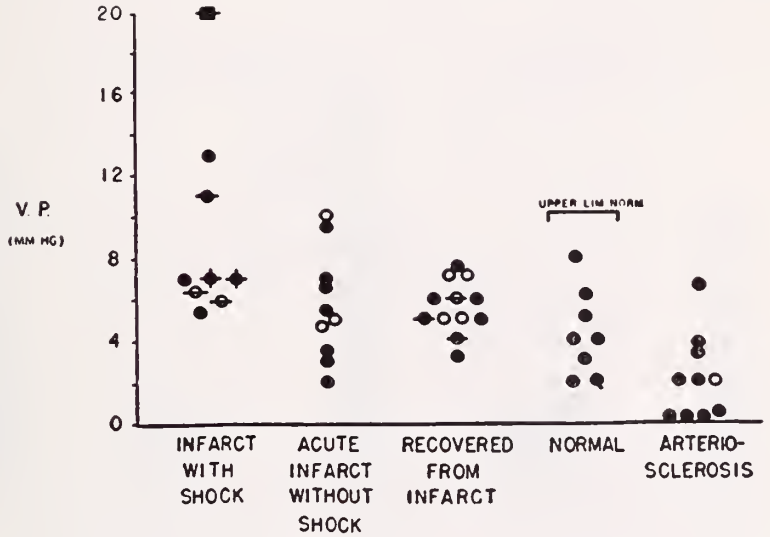

Fig. 2. Alterations in venous pressure in human subjects with acute myocardial infarction with and without shock. There is little difference between the two groups. (From Smith, W. W. *et al.*, Circulation 9: 352, 1954. Reprinted by permission of The American Heart Association, Inc.)

pronounced increase. There was no rise in intracardiac pressures in these animals studied for five hours to indict congestive heart failure as the principal mechanism, although studies several hours later might demonstrate some rise in blood volume and venous pressure, suggesting that even if heart failure may occur later in the course of shock, it is not essential for its production. As mentioned previously, however, Case has found elevated left atrial pressures in open-chest animals (some of which were vagotomized), shortly after coronary constriction (9).

The pathogenesis of shock following myocardial infarction may be further studied by attempts to increase central aortic pressure by extracorporeal circulatory support in experimental myocardial infarction with shock. Our investigations (Table II) have shown that shunting of large volumes of blood from the superior vena cava into the aorta produces no rise in central aortic pressure (14).

The failure to raise central aortic pressure by by-passing the heart and shunting large volumes of blood into the aorta suggests that congestive heart failure with venous pooling is not the principal cause of the aortic hypotension in these animals. However, when systemic vascular resistance is mechanically increased by occluding the abdominal aorta with a balloon catheter, supplying the distal aorta below the obstruction with blood from the superior vena cava, there is a considerable rise in central aortic pressure (Fig. 3).

Assuming that factors regulating systemic vascular resistance are of im-

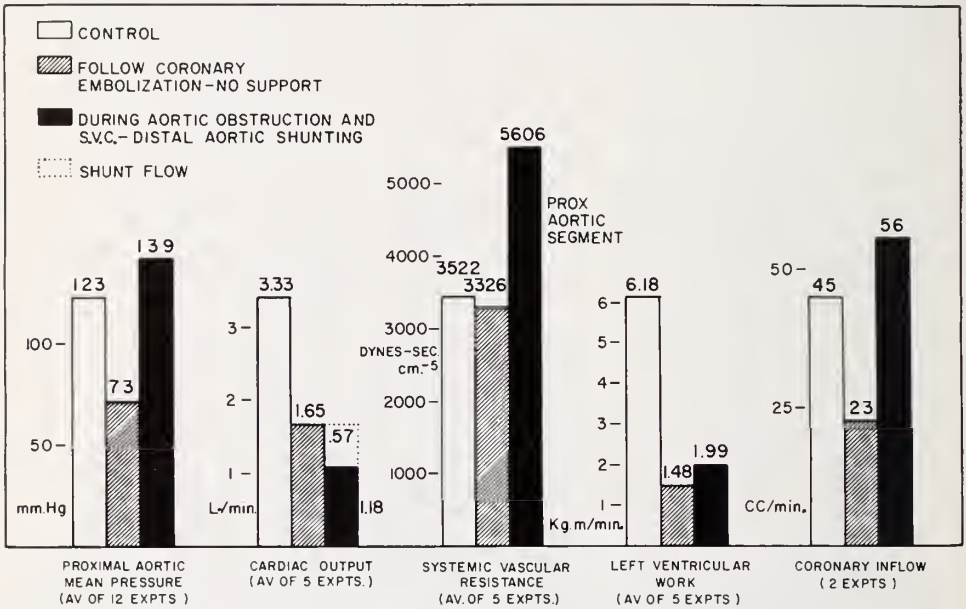

FIG. 3. Hemodynamic changes produced by coronary embolization in dogs and the effect of superior vena caval-distal aortic shunting. Following coronary embolization, there is a fall in cardiac output and aortic pressure while systemic vascular resistance remains unchanged. During abdominal aortic obstruction and superior vena caval-distal aortic shunting, there is considerable rise in central aortic pressure, attributable to the mechanical increase in vascular resistance in the proximal aortic segment. (From Kuhn, L. A. *et al.*, American Journal of Cardiology 7: 218, 1961. Reprinted by permission of The American Journal of Cardiology.)

portance in the genesis of coronary shock, is there any evidence as to what specific factor may be involved? That a reflex is involved is suggested by experimental studies which reveal greater falls in arterial pressure after coronary occlusion in the animal with a denervated heart than in the intact animal (11). There is no evidence that this is due to a vagal reflex as experimental shock may occur after bilateral vagotomy (7). Cutting the posterior roots of T1-T5 in the dog results in a prompt rise in peripheral resistance and arterial pressure (7). This suggests the possibility of a reflex arising from the injured area which inhibits normal homeostatic mechanisms acting on the systemic vascular resistance. It has not been determined whether this mechanism applies to humans.

Thoracic epidural analgesia has been used in a few patients with myocardial infarction with shock with some beneficial result in regard to potentiating or restoring responsiveness to vasopressor agents (7). However, this method has not been used widely enough to form an accurate opinion as to its efficacy.

The data from both human subjects and experiments simulating to a certain extent the hemodynamic alterations found in humans indicate that shock following myocardial infarction is initiated by a precipitous fall in cardiac output.

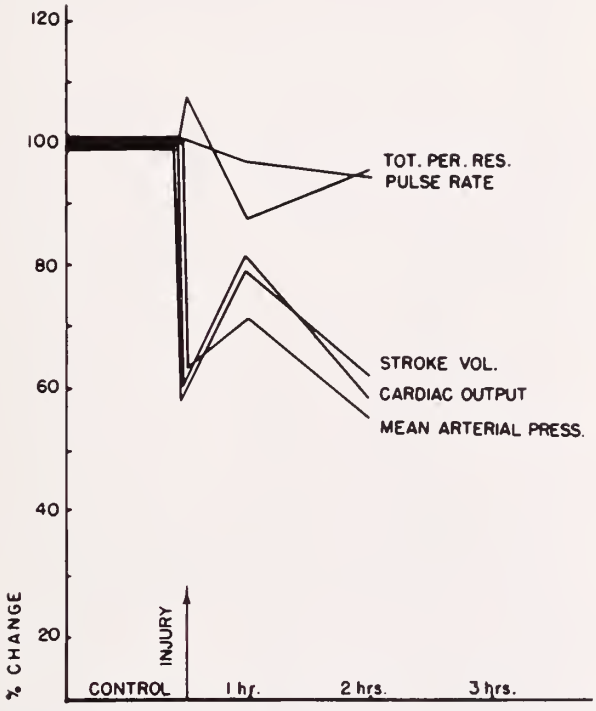

Fig. 4. Hemodynamic alterations in dogs with acute myocardial infarction due to plastic sphere coronary embolization which developed shock. There is a precipitous fall in cardiac output but systemic vascular resistance does not show a compensatory rise and there is resultant aortic hypotension. (From Agress and Binder, American Heart Journal 54: 458, 1957. Reprinted by permission of the C. V. Mosby Co., Inc.)

There is then, in some individuals, sufficient compensatory arterial vasoconstriction to maintain adequate arterial pressure but in others, for reasons that are not known, this does not occur. This leads to further hypotension, reduced coronary and cerebral perfusion pressure and further deterioration of the heart and other vital organs and in some cases, to the syndrome of congestive heart failure. Whether organ hypoxia then leads to release of vasodepressor substances or circulatory inadequacy of sufficient magnitude to result in thrombotic capillary occlusion of vital organs, as in other forms of shock, has not been definitely established. It should be realized that it is unlikely that "coronary" shock is attributable to the same mechanism in all patients as in many, severe congestive

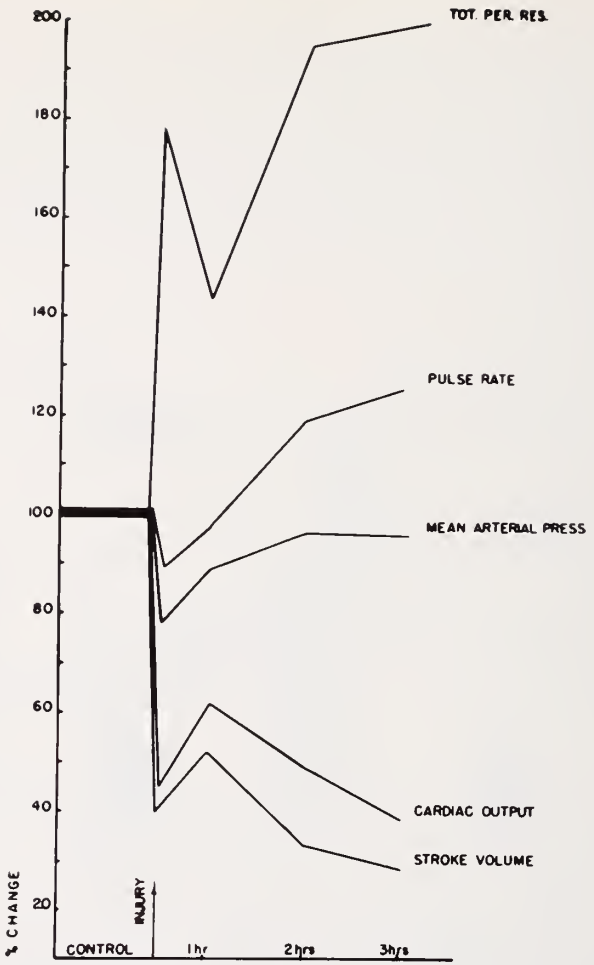

FIG. 5. Hemodynamic alterations in dogs with acute myocardial infarction due to plastic sphere coronary embolization which did not develop shock. Although the cardiac output fell to levels as low as the outputs in the animals which developed shock (Fig. 4), the systemic vascular resistance in this group without shock shows a pronounced increase and aortic pressure is well maintained. (From Agress and Binder, American Heart Journal 54: 458, 1957. Reprinted by permission of the C. V. Mosby Co., Inc.)

heart failure dominates the clinical picture from the beginning, in others it may develop as a late complication, whereas in others it may not be apparent at all.

TREATMENT

One of the fundamental aims in the treatment of myocardial infarction with shock has been to raise the arterial pressure. It has been established that coronary perfusion pressure is a major determinant of coronary flow, the increase of which increases the blood supply to ischemic as well as normal areas of the myocardium and improves the function of both ventricles (9, 15). It would also be advantageous if the contractile power of the myocardium were increased and if

this were not accompanied by a dangerous arrhythmia or an increase in left ventricular work too strenuous for the compromised left ventricle.

With few exceptions (16–18) several studies have indicated that vasopressor agents have improved prognosis in myocardial infarction with shock. Most patients have been treated with norepinephrine. Results in 200 of these (reviewed by Malach (17) (Table III) indicate a pressor effect in 75 per cent, relief of shock in about one-half and about a 60 per cent mortality, compared to a mortality in untreated subjects of close to 100 per cent. Differences in criteria for "shock" and varying delay prior to treatment may account for some of the reported

TABLE II

The effect of superior vena caval-aortic shunting of large volumes of blood on the thoracic aortic pressure in normal dogs and in those with acute myocardial infarction

(From Kuhn, L.A. *et al.*, Circulation Research 8: 199, 1960. Reprinted by permission of The American Heart Association, Inc.)

	Normal dogs mm Hg (mean)		Flow cc/Kg./min.
	Control	During shunt	
	140/115 (125)	130/105 (115)	59
	130/90 (95)	150/90 (100)	51
	150/115 (127)	155/120 (132)	58
	160/110 (125)	140/90 (110)	27
Av.	145/108 (118)	144/101 (114)	49
	Following coronary embolization		
	105/70 (80)	110/80 (90)	50
	110/60 (75)	110/70 (80)	46
	120/90 (100)	90/70 (80)	60
Av.	112/73 (85)	100/73 (83)	52

differences in mortality. The prognosis is considerably improved if treatment is begun within three hours of the onset of shock (19–21). Therefore it may probably be concluded that maximal vasoconstriction has not occurred in many patients and that the net effect of vasopressor therapy is beneficial despite any theoretical dangers attributable to myocardial (22, 23) and hepatic damage, increased cardiac work attendant upon the rise in arterial pressure and interference with regional circulation due to vasoconstriction. The use of other vasopressor agents, principally metaraminol (Aramine) (24, 25), and, to a lesser extent methoxamine (Vasoxyl), phenylephrine (Neosynephrine) and mephentermine (Wyamine) has not been as extensive as that of norepinephrine. Of all of these, reported experience has perhaps been most extensive with metaraminol, with results similar to those with norepinephrine. Favorable results have also

been reported with mephentermine which has a central action and also causes peripheral venoconstriction (26). Occasionally, patients have been reported who do not respond to metaraminol or mephentermine but do to norepinephrine.

Conclusions based on the efficacy of pressor agents in improving prognosis in myocardial infarction with shock are only of partial aid in elucidating its mechanism. It has been established that different vasopressor agents have differing central and peripheral effects, ranging from those with predominantly peripheral effects (methoxamine) to those with myocardial and little peripheral effect, such as mephentermine. The two agents which have been most utilized in humans with myocardial infarction with shock, norepinephrine and metar-

TABLE III

Results of treatment of acute myocardial infarction with shock with norepinephrine

These have been compiled from the investigations of several authors by Malach and Rosenberg (17). (Reprinted by permission of The American Journal of Cardiology.)

No. of cases	Pressor effect		Relief of shock		Mortality	
	No.	%	No.	%	No.	%
7	4	57	1	14	6	86
14	10	71	9	64	10	71
13	9	70	4	31	11	85
14	12	85	6	42	8	58
6	5	83	1	17	5	83
9	8	88	5	56	4	44
6	6	100	4	67	2	33
7	7	100	7	100	1	14
30	19	63	17	57	—	—
30	27	90	20	67	14	47
25	23	92	12	48	17	68
22	10	45	—	—	22	100
17	10	59	7	41	17	100
Totals 200	150	75	93	47	117	59

aminol, have both central and peripheral actions. Evidence is somewhat conflicting as to which of these sites of action is most important. These agents have shown increase in contractile force of both ventricles as well as increase in systemic vascular resistance (27, 28). In addition, available oxygen to the myocardium is increased (29) and there is probably systemic venoconstriction (30). The increase in coronary flow seen with norepinephrine (31) may be due to direct vasodilatation of the coronaries, increased perfusion pressure secondary to the systemic vasoconstriction or to inotropic effects producing a prompt relaxation of the ventricular muscle and comparative lengthening of diastole as well as more complete emptying of venous and capillary beds by more forceful systole.

In animals, there is some evidence that the central cardiac effect may be of benefit in the relief of cardiogenic hypotension. In dogs with acute myocardial

infarction and hypotension, Guzman has reported that the arterial pressure rise produced by methoxamine, which presumably acts solely peripherally, was associated with a rising left atrial pressure whereas equipressor doses of norepinephrine did not produce this, suggesting that an agent which acts both centrally and peripherally may have greater advantage than one which acts solely to increase systemic vascular resistance (32). However, the fact that the substance acting solely peripherally did cause an arterial pressure rise is further evidence of the importance of peripheral vascular factors in cardiogenic hypotension. Sarnoff has also studied this problem in dogs, utilizing metaraminol (33). He established that initial improvement in left ventricular function after metaraminol administration in cardiogenic hypotension was related directly to central effects. During an initial period of aortic pressure rise cardiac output fell slightly and left atrial pressure increased. Subsequent to this, during the period central effects were evident, cardiac output rose, producing further rise in aortic pressure and fall in left atrial pressure.

Before accepting these results as indicating that a central effect is most important in the relief of cardiogenic shock by these agents, it should be realized that in the dog arterial pressure increase with norepinephrine can be caused independently of cardiac output changes (31) and that there is no definite relationship between increasing contractile force, which is the principal central effect of these agents and improving cardiac output, which is affected by several other factors (34). In fact, there is evidence that cardiac output is not increased at all by norepinephrine in the dog (35) or human subject (36, 37).

Recently reported experimental studies by Aldinger have demonstrated that in the dog the major determinant of the increased coronary flow during levarterenol administration was the increased head of pressure in the aorta with increases in ventricular contractile force related only minimally to increases in coronary flow, again indicating the importance of the peripheral effects of this drug (38). The issue must be considered as unsettled at this time until large series of humans with myocardial infarction with shock are studied with appropriate hemodynamic measurements, utilizing various drugs with different sites of action.

Although neither the mechanism of shock following acute myocardial infarction nor the site of action of drugs used in its treatment have been elucidated fully these questions may prove to be of considerable clinical importance in the future. With the development of various technics of temporary support of the circulation, it may be anticipated that attempts to apply these methods to selected human subjects with acute myocardial infarction with shock will be undertaken. The precise technic to be utilized and its ultimate success, whether veno-arterial shunting, left heart by-pass, "counterpulsation" with delivery of blood into the aorta during diastole, increase in systemic vascular resistance by balloon obstruction of the abdominal aorta with superior vena caval-distal aortic shunting, all of which have been employed successfully in the laboratory, may ultimately depend on firm knowledge of the hemodynamic alterations which occur in this syndrome.

SUMMARY

Experimental and clinical studies relating to the hemodynamic alterations occurring in acute myocardial infarction with shock have been reviewed.

The precise mechanism of production of shock following acute myocardial infarction has not been elucidated fully. Relatively limited clinical studies in human subjects have demonstrated consistently a fall in cardiac output, but there have been some patients with equally severe reductions in cardiac output who have not developed significant aortic hypotension. Although the syndrome of congestive heart failure may coexist with or follow that of shock, many patients with shock have neither the clinical signs nor hemodynamic manifestations of congestive heart failure, suggesting that the presence of heart failure is not always essential for the production of shock.

Laboratory investigation has been hampered by the difficulty in producing this syndrome experimentally. From experiments with plastic sphere coronary embolization in dogs, support is gained for the concept that factors regulating systemic vascular resistance are of importance in the genesis of shock following acute myocardial infarction. These experiments have demonstrated that cardiac output may fall equally in the animals which develop shock as compared to those which do not, but that in the animals developing shock, there is failure of systemic vascular resistance to rise appropriately in response to the diminished cardiac output. In contrast, animals which do not develop shock show considerable increases in systemic vascular resistance. In addition, the aortic hypotension following experimental acute myocardial infarction is unchanged by prolonged veno-arterial shunting of large volumes of blood, but is promptly reversed by mechanically increasing systemic vascular resistance by means of a balloon catheter inserted into the abdominal aorta.

Although vasopressor therapy has been moderately effective in reducing mortality from myocardial infarction with shock, particularly if utilized promptly, the more commonly used agents act both centrally and peripherally. While some evidence has been developed in animals that the central, direct cardiac effects are of primary importance in relieving the shock-like state, this issue should be considered unsettled until large series of human subjects are studied, utilizing agents with different sites of action.

There is some evidence that the mechanism of shock may differ among individuals. Rational application of any one of a variety of technics of temporary circulatory support in such individuals depends on precise knowledge of the hemodynamic alterations.

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Pregnancy in Unmarried Women, Medical and Social Characteristics*

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The problems inherent in extramarital pregnancies long have been of concern to the community medical and social agencies. Such pregnancies account for an increasing proportion of our birth rate. For the country as a whole the recorded rate increased from 3.6 per cent of all live births in 1947 to 5 per cent (more than 200,000) of all live births in 1958 (1). An even sharper increase occurred in New York City, rising from 3 per cent in 1946 to 8 per cent in 1959, representing 13,500 known out-of-wedlock newborn (2).

A study was undertaken at The Mount Sinai Hospital covering all registered, known unmarried women who were served in the Obstetrical Pavilion during the calendar years 1956 and 1957. The purpose of the study was to determine social characteristics, medical findings, use of hospital services and use of social agencies, by this group of women. The definition of extramarital pregnancy which was used is a pregnant woman who was not legally married to the father of the prospective child at the time she registered for prenatal care. This includes women of divorced, separated, widowed or common-law status, and women who married after registering for prenatal care.

The group studied totalled 227 women pregnant out-of-wedlock and constituted 6.7 per cent of the patients receiving care in the Obstetrics Clinic and Ward during the study period. The percentage is only slightly less than the 8 per cent unmarried pregnancies which prevailed for New York City as a whole in 1959. Pregnant unmarried women cared for on the private service were not included by and large because of the difficulty in identifying them by the study method.

Confirming the findings of other recent studies of unmarried mothers in New York City, The Mount Sinai Hospital group shows a wide range of social characteristics. Rather than establishing an "average" unmarried mother, the data show that there are wide variations.

There were a few factors which exercised a selective influence on the characteristics of the women who received care at Mount Sinai Hospital. These factors included: the largely Puerto Rican and Negro composition of the population

* Based on findings in "A Review Of Medical And Social Characteristics of Out-Of-Wedlock Pregnancies at The Mount Sinai Hospital," a study completed under a grant from the Robert Sterling Clark Foundation.

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(A second article, "Pregnancy in Unmarried Women, their Planning for Newborn and Use of Social Services" will appear in "Children," U. S. Department of Health, Education and Welfare, Social Security Administration, Children's Bureau.)

in the geographical area of the hospital; the proximity of a shelter for unmarried mothers which referred patients, most of whom were white women and many of whom came to New York City for care and seclusion during their pregnancies; and finally, The Mount Sinai Hospital admissions policy which gives priority to women who apply before their seventh month of pregnancy and thus, in effect, excludes most women who tend to be very late in seeking prenatal care.

Some highlights of the social characteristics of the unmarried mothers treated at Mount Sinai Hospital follow: The ethnic distribution was almost a 4–3–3 ratio among Negro, white and Puerto Rican women respectively. The age distribution of the group appears to substantiate that unmarried motherhood is predominantly a phenomenon of younger women. Almost half of the women had been pregnant before. Of this number the larger percentages were in the Negro and Puerto Rican groups. Statistically, only one-third of the women came from "intact" family units. "Broken families" in relation to unmarried motherhood is an area requiring study in depth, including the meaning of "intactness" where a husband and wife are living together. Less than one-quarter of the women were born in New York City. However, over four-fifths were residents prior to conception but with wide variations according to ethnicity—100% Puerto Rican, 95% Negro, and 50% white. There were marked differences in their living arrangements at the time of conception: about one-third were living with their parent(s), one-quarter with putative fathers, and another two-fifths were living alone or with relatives or friends. These figures follow ethnic lines with white women predominantly living with their parent(s), Puerto Rican women, with the putative fathers and Negro women largely alone, or with relatives or friends. The phenomenon of Puerto Rican women living with putative fathers reflects the high number of consensual unions as characteristic of this group, and not the Negro or white groups. As might be expected the younger girls of all ethnic groups live with their parent(s). About forty per cent of the women made a change in living arrangements during their pregnancy. This is accounted for primarily by the white group who most frequently left their home for care in shelters. The majority of the study group, during pregnancy were either self-supporting, or supported by families, putative fathers, or friends. The non-resident group was entirely supported through private resources. Only a little more than one-quarter of the 227 women received assistance from the Department of Welfare, with a small additional number requiring such help later on for the support of themselves and the child. Since the Negro and Puerto Rican groups as prior residents of New York City met the financial eligibility requirements for clinic care, it can be assumed their economic level was in the lowest third. On the other hand, the high percentage of migration among the whites carries with it the probability of a change in economic status in the use of clinic care. Of interest in a further study would be a comparison between the socio-economic factors of migrating and nonmigrating white women.

It has been the assumption of obstetrical services that the factor of unmarried motherhood does not affect the patient's obstetrical course. The findings of this study validate the assumption. Differences in medical need within this group

are much more apt to originate in the socio-economic factors attendant to ethnicity. Differences in use of medical care on the other hand are more apt to reflect the social situation of the unmarried mother.

An important aspect of the study was the review of gross signs of medical complexity or difficulties among women pregnant out-of-wedlock. A number of general indices was used for this purpose, including incidence of nausea, anemia, toxemia and medical complications requiring special attention at other clinics or by hospitalization. Other indices considered were duration of labor, weight gain, temperature elevation, comparison of actual delivery date with the expected delivery date and perinatal mortality.

Nausea is a common phenomenon in pregnancy. The incidence in The Mount Sinai Hospital study group was slightly higher than for the married population. About half (48%) of the women reported nausea during the first trimester of their pregnancy, and with relatively slight variation among the ethnic groups (Table I). White women were the highest, with 52 per cent. For the Negro and Puerto Rican women, the percentages were 43 per cent and 49 per cent respectively. The separated, widowed, or divorced group showed the highest incidence, with 84 per cent of these reporting nausea. The lowest incidence was reported by the common-law relationship group (32%) and the pregnancy marriage group (37%). These figures for the incidence of nausea in the unmarried mother differ markedly from the observation of the absence of nausea reported in an earlier study done by Leontyne Young (3).

Anemia occurred among 39 per cent of the women, this included 28 per cent who had mild anemia, 8 per cent who had moderate anemia and 3 per cent who had severe anemia. The definition of anemia was arbitrarily set with a hemoglobin level for mild at 9.5–10.5 Gm, moderate at a level of 8.0–9.4 Gm, and severe at under 8.0 Gm. There is a significant variation among ethnic groups; 48 per cent of the Negro and 49 per cent of the Puerto Rican women had anemia as compared with 17 per cent for the white group. These figures, while high, appear consistent with the clinic population groups. The lower anemia rate for the white group is a reflection of their higher socio-economic status.

Toxemia was recorded for 17 (or 8%) of the women. Of these, all but two had toxemia to a mild degree. The toxemia incidence for the ward service as a whole at The Mount Sinai Hospital between 1953 and 1957 was a comparable 7.5 per cent (4).

Dr. Pakter *et al.* in a study of unmarried mothers in New York City noted that, "Toxemia of pregnancy (eclampsia and preeclampsia) was the most frequent complication recorded. This was true for both the married (2.0%) and unmarried (3.1%)" (5). The disparity between The Mount Sinai Hospital figure and that of the Pakter group can be explained by the fact that our toxemia incidence figure was derived from the antepartum chart and hospital record. The Pakter group figure was derived from the New York City birth certificates. It is a fair assumption that more often only patients with severe toxemia or perhaps significant intrapartum toxemia would be recorded as such on the birth certificate. (6).

Twenty pounds is considered the maximum weight gain desired during pregnancy and nineteen pounds was the median weight gain over the stated non-pregnant weight for the 210 women for whom weight gain data were recorded. Fifty-five per cent showed a weight gain of 20 pounds or less, 35 per cent a gain of 21 to 30 pounds, and 10 per cent a gain of more than 30 pounds. There is a slight variation by age, and ethnic group. The "16 to 18," and the "34 and over" age groups, for example, gained less weight than the overall average, with 66 per cent and 67 per cent respectively gaining 20 pounds or less. The Puerto Rican group showed an average weight gain (*i.e.* 55% gained 20 pounds or less) whereas the white group tended to gain more (only 46% kept within 20 pounds) and the Negro group gained less (with 61% within 20 pounds). There was variation according to civil status also, with 46 per cent of the "separated, widowed or

TABLE I

Unmarried Mothers, by Incidence of Nausea during Pregnancy and Ethnic Group, The Mount Sinai Hospital

1956–1957

Ethnic Group	All unmarried mothers*	Unmarried mothers who reported nausea	
		Number	Per cent of total in ethnic group
Negro	88	38	43
White	71	37	52
Puerto Rican	67	33	49
All ethnic groups	226	108	48

* Excludes 1 unmarried mother for whom information on incidence of nausea was not known.

divorced" within the 20 pound gain, but 60 per cent of the women with common-law relationships staying within this range.

Syphilis was found to be the second leading specific complication among the unmarried (1.5%) and an infrequent complication among the married women (0.5%) in Dr. Pakter's study. There was no syphilis in the small Mount Sinai Hospital study group.

Medical complication of various kinds, requiring referral to other clinics or in-hospital care, appeared in 82 (or 37%) of the cases (Table II). Most of the women (67) could be treated as ambulatory patients at other clinics. Of the remaining fifteen, 5 required surgery and 7 required hospitalization without surgery and 3 required a combination of services.

Forty-three per cent of the Negro women had such medical complications, in contrast to 39 per cent for the Puerto Rican, and 26 per cent for the white groups. This is approximately the same incidence of medical complication seen in The Mount Sinai Hospital Prenatal Clinic. The high incidence includes referral to Cardiac Clinic for evaluation of possible physiological murmurs and

to Hematology Clinic for investigation for anemia. The ethnic variations reflect that the white patients came from a higher socio-economic group.

Comparing medical complications of married and unmarried pregnant women, Dr. Pakter *et al.* noted that "though the unmarried within each ethnic group had a slightly higher frequency of complications than the married, ethnic derivation was more significant than marital status. The fact that the married nonwhites had a greater frequency of complications than the unmarried whites

TABLE II

Unmarried Mothers, by Medical Complications during Pregnancy, and Ethnic Group, The Mount Sinai Hospital

1956–1957

Nature of medical complication	All ethnic groups*	Ethnic Group		
		Negro	White	Puerto Rican
Medical complications requiring—				
treatment as ambulatory patient in other clinics	67	29	17	21
hospitalization (but no surgery)	7	4	—	3
surgery	5	3	1	1
combination of treatment	3	2	—	—
total medical complications requiring treatment:				
number	82	38	18	26
per cent	37%	43%	26%	39%
No medical complication:				
number	142	50	52	40
per cent	63%	57%	74%	61%
Total				
number	224	88	70	66
per cent	100%	100%	100%	100%

* Excludes 3 unmarried mothers for whom information on medical complications and ethnic group was not known.

indicates that complications of pregnancy are more likely to occur in the ethnic group known to be deprived" (5).

Generally, the unmarried mothers did not show prolonged labor. The experience with The Mount Sinai Hospital group is comparable to any group of women in labor. About 7 out of 10 (69%) of the women were in labor for ten hours or less; three out of 10 were in labor between 11 and 24 hours. Only three women (out of the group of 216 for whom data are available) were in labor more than 24 hours (Table III). There was of course variation according to parity. Only 60 per cent of the primiparas were in labor ten hours or less as compared with 85 per cent and 78 per cent for those multiparas who had one, or more than one previous pregnancy respectively.

TABLE III

Unmarried Mothers, by Duration of Labor, Number of Previous Pregnancies and Ethnic Group, The Mount Sinai Hospital

1956–1957

Number of previous pregnancies and ethnic group	Total*	Duration of labor, in hours		
		10 or less	11–24	25 or more
No previous pregnancy				
Negro	47	27	19	1
White	54	39	15	—
Puerto Rican	24	8	14	2
total				
number	125	74	48	3
per cent	100%	60%	38%	2%
One previous pregnancy				
Negro	14	10	4	—
White	10	10	—	—
Puerto Rican	9	8	1	—
total				
number	33	28	5	—
per cent	100%	85%	15%	
Two or more previous pregnancies				
Negro	24	19	5	—
White	4	4	—	—
Puerto Rican	30	23	7	—
total				
number	58	46	12	—
per cent	100%	78%	22%	
Total				
Negro				
number	85	56	28	1
per cent	100%	66%	33%	1%
White				
number	68	53	15	—
per cent	100%	78%	22%	—
Puerto Rican				
number	63	39	22	2
per cent	100%	62%	35%	3%
Grand Total				
Number	216	148	65	3
Per cent	100%	69%	30%	1%

* Excludes 11 unmarried mothers for whom information on duration of labor, ethnic group and number of previous pregnancies was not known.

Thirty-eight (or 18%) of the women showed a temperature elevation either on admission, or after delivery, or both before and after delivery including "one-day" fever. Most of them showed the temperature rise after delivery (31). The variation in ethnic groups ranged from only 7 per cent showing a temperature rise in the white group, to 21 per cent and 24 per cent respectively for the Puerto Rican and Negro groups. The percentage of temperature elevation for The Mount Sinai Hospital Obstetrical Ward Service is 12.1 per cent (4). We can offer no explanation for the difference between the 18 per cent for the study group and the 12.1 per cent for the total Obstetrical Ward Service.

TABLE IV

Unmarried Mothers, by Neonatal Status of Issue and Ethnic Group, The Mount Sinai Hospital

1956–1957

	All unmarried mothers* total	Negro	White	Puerto Rican
Full-term normal	198	72	64	62
Stillborn term	2	2	—	—
Neonatal death term	1	1	—	—
Abortion	6	2	—	4
Therapeutic abortion	5	1	3	1
Stillborn premature	2	1	1	—
Neonatal death premature	0	—	—	—
Prematurity	12	9	3	—
Total	226	88	71	67

* Excludes one unmarried mother for whom information on neonatal status of issue and ethnic group was not known.

The "actual delivery date" fell within 14 days of the "expected delivery date" in 70 per cent of the cases, and within 21 days in 80 per cent of the cases. In 15 per cent, the difference between the two dates was over 28 days. The variation between ethnic groups was negligible; for 79 per cent of the Negro, 83 per cent of the white and 76 per cent of the Puerto Rican women the two dates were within 21 days of each other. The method of delivery for these patients showed no variation from The Mount Sinai Hospital group as a whole.

There were no maternal deaths among the relatively small sample of The Mount Sinai group of unmarried women. The uncorrected fetal mortality for Mount Sinai Hospital 1953–57 was 2.94 per cent. The figure for our small series calculated on the same basis would be 2.37 per cent showing no significant difference between the unmarried and the married mothers at The Mount Sinai Hospital in terms of fetal survival. Four of the fetal mortalities were in the Negro, one in the white and none in the Puerto Rican group (Table IV). Dr. Pakter *et al.* report a maternal mortality rate of 5.0 per 10,000 live births for the married, and a rate four times as great (21.3 per 10,000 live births) for the un-

married. The unmarried whites had the highest death rate (27.0 per 10,000). This was attributed to the much higher incidence of illegal abortion among unmarried as compared with the married; their findings showed that more than two-thirds of the deaths among the unmarried were caused by abortions. These data suggest the desirability of further study, at The Mount Sinai Hospital, of patients with self-induced or spontaneous abortions.

Twenty weeks is considered the latest time for commencing adequate prenatal care for a normal healthy woman. Forty-two per cent of the women made their first visit to the Prenatal Clinic by the 20th week of their pregnancy; this includes the 9 per cent who came by their 12th week.

Forty-six per cent came between their 21st and 30th week, with the remaining 12 per cent arriving after their 31st week. There are striking contrasts according to ethnic groups; 80 per cent of the white women came after their 20th week; this includes 19 per cent who arrived after their 31st week. By contrast 52 per cent of the Negro and 46 per cent of the Puerto Rican women arrived after the 20th week (Chart 1). The relatively later start of prenatal care by the white women is related to nonresidence.

Dr. Pakter *et al.* report that 6.6 per cent of the unmarried and 45.7 per cent of the married women received medical care in the first trimester. Among the unmarried women, 50.3 per cent started prenatal care after the sixth month of pregnancy (which is regarded as too late for optimal prenatal care). Their data showed that ethnic group, as well as marital status reflected given patterns of prenatal care. "Among the whites, 36.7 per cent of the unmarried received care in the first six months as compared with 87.2 per cent of the married. Among the non-whites, 42.9 per cent of the unmarried received care in the first six months as compared with 61.7 per cent of the married. Among the Puerto Ricans, 43.5 per cent of the unmarried received care in the first six months as compared with 60.4 per cent of the married. These data indicate that the white married women (87.2%) had the highest proportion of timely prenatal care (within the first six months). The unmarried in each ethnic group had a lower proportion of timely prenatal care than the married" (2).

Thus a comparison of the time lapse in starting prenatal care in the two studies suggests that The Mount Sinai Hospital group tended to come somewhat earlier than the unmarried mothers in the city as a whole. The other observation is that both studies reveal the polarity between unmarried whites and married whites in securing prenatal attention.

Of the 38 women who moved to New York City after conception, only 14 (or 37%) arrived during their first trimester of pregnancy. The remaining 24 women arrived during the second trimester, or later. Thus, the nonresidents tended to make their first visit to the clinic later than the residents. This is further illustrated by the fact that while almost half (47%) of the residents made their first visit by their 20th week, only one-quarter (24%) of the nonresidents reported by this interval.

Another aspect of this is the fact that only 19 per cent of the shelter referrals made their first visit by the 20th week. This is a reflection of the large (60%)

out-of-city population of the shelters who tended to migrate to New York City during their second trimester of pregnancy or later. Information is available for the 54 women on the length of time they resided at the shelter. More than half

CHART 1

Number and Percentage of Unmarried Mothers, by Duration of Pregnancy at First Visit to Mount Sinai Hospital, by Age and by Ethnic Group

1956–1957

Ethnic group and age of the unmarried mother	Duration of pregnancy	
	20 weeks or less	21 weeks or more
Negro		
15 or under	▮▮▮	▮▮▮▮
16–18	▮▮▮▮▮▮▮▮▮	▮▮▮▮▮▮
19–21	▮▮▮▮▮▮▮▮▮	▮▮▮▮▮▮▮▮▮▮▮▮▮
22–33	▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮	▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮
34 or over	▮▮▮	
total		
number	43	42
per cent	51.5%	48.5%
White		
15 or under		▮▮
16–18	▮▮	▮▮▮▮▮▮▮▮▮▮
19–21	▮▮▮	▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮
22–33	▮▮▮▮▮▮▮▮▮	▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮
34 or over		
total		
number	14	56
per cent	20%	80%
Puerto Rican		
15 or under	▮▮	
16–18	▮	▮▮▮▮▮▮
19–21	▮▮▮	▮▮▮▮▮▮▮
22–33	▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮	▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮
34 or over	▮▮▮	▮▮
total		
number	36	31
per cent	54%	46%
Total		
number	95	129
per cent	42%	58%

Each ▮ represents one patient.

(57%) stayed at the shelter 4 months or more, 15% resided from 3–4 months, and 11% 2–3 months. Seventeen per cent were there less than 2 months; this includes 13 per cent who were there less than one month. Incidentally, while the data show that a high proportion of the women arrived at the shelter fairly late, the data also suggest the possibility that those who stay there could be

referred earlier to prenatal care. For example, while 23 women entered the shelter before their 20th week of pregnancy, only 8 were referred to the clinic within this interval.

Dr. Pakter *et al.* note that "a somewhat higher proportion of nonshelter women (42.5%) received prenatal care in the first six months of pregnancy as compared with the shelter group (35.7%). This may be due to several factors. In a number of shelters early prenatal care may be given by a doctor outside the hospital clinic, and thus may not be reported on the birth certificate by the hospital of delivery. Another possibility may be that the unwed expectant mother delays seeking care due to reticence and does not enter the shelter until relatively late in her pregnancy. This pattern of relatively late prenatal care was found to be true of all receiving shelter care, regardless of ethnic group" (2).

Fifty-three per cent of the women who were previously pregnant reported within 20 weeks, whereas only 34 per cent of those with no previous pregnancies came within this same period. This also probably relates to the fact that the shelter group was basically a no previous pregnancy group.

There does not seem to be a significant relationship between the multipara's living arrangements and inception of prenatal care. About 4 out of 10 of the women who lived alone, or with the putative father, or with friends or relatives, reported to the clinic by their 20th week of pregnancy. Three out of 10 of the women who lived with their own parent(s) reported within that time. The one exception is found among the 5 girls (4 of whom were white and 1 Negro) who were living at educational institutions; only 1 came within the 20th week, while 4 reported between the 21st and 30th week.

Separated, divorced and widowed women tended to arrive earlier; 27 of the 31 women in this group (or 87%) came to the clinic by their 20th week. This is consistent with the fact that 25 of the 31 (or 80%) women in this group were previously pregnant.

Based on face-to-face interviews with 520 unmarried mothers in which deterrents to early medical care were explored, Bernstein and Sauber report that: "In the judgment of the interviewers, the main deterrents to care, in order of importance, are that the women see no need to get care earlier or at all (20%), that they try to conceal their pregnancy as long as possible (18%), that they find it inconvenient because they are caring for children at home, or for other reasons (16%), that they are reluctant to give up or take time off from their jobs (12%), that they do not know they are pregnant (9%), that they cannot pay the costs of care by a private physician (7%), or finally, that clinic intake requirements at the clinic where service is requested make them ineligible (6%)" (7).

The median number of visits to the Prenatal Clinic prior to confinement was seven. Since the white group tended to come for their first visit later than the others, it is expected that they would have fewer total visits. The median number of visits was 6.7 for white, 6.9 for Puerto Rican, and 8.5 for Negro women. For optimal prenatal care, it is expected that a normal healthy woman would

make about 12 visits to the Prenatal Clinic. By this standard, almost seventy per cent of the women had less than optimal prenatal care.

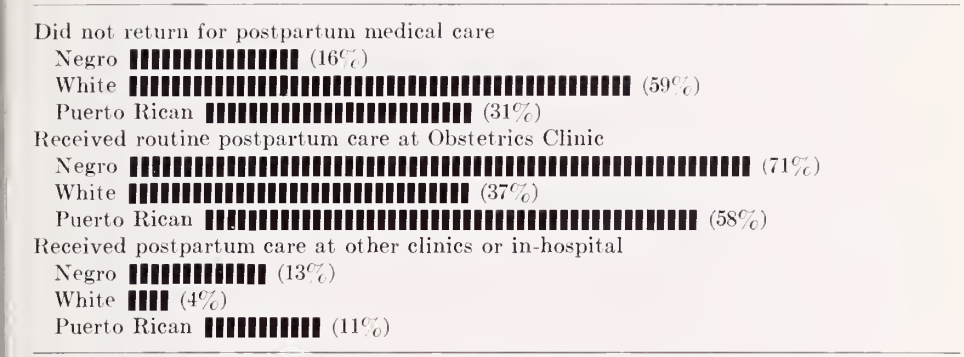
Postpartum care is considered essential to protect the health of the mother, and all patients are expected to report to the Postpartum Clinic at least once within six weeks after delivery. If the medical condition requires it, visits to other clinics or hospitalization may also be prescribed. At Mount Sinai Hospital the postpartum care had special significance in helping to prevent subsequent unwanted pregnancies. At present, it is only during the postpartum visit that birth control information is offered.

More than half (57%) of the women returned for routine postpartum care. An additional 10 per cent received medical attention: at the Gynecology Clinic

CHART 2

Percentage Distribution of Unmarried Mothers Returning for Postpartum Medical Care, by Ethnic Group, The Mount Sinai Hospital

1956–1957



Each ▮ represents 1% of ethnic group. (Accommodated to space.)

(2%), other clinics (6%), and in the hospital (2%). The remaining one-third (33%) did not return for any check-up following their discharge from hospital.

There were significant variations according to ethnic group (Chart 2). Sixteen per cent of the Negro women did not return for postpartum care as compared with 31 per cent of the Puerto Rican and 59 per cent of the white women who did not return. Seventy-four of the 99 women (or 75%) who were previously pregnant returned for the postpartum care; this compares with 61 per cent of the primiparas who returned. The low figure for the primiparas is due in part to the large number of out-of-town white women. Seventy-one per cent of the New York City residents returned for postpartum care in contrast to only 46 per cent of the nonresidents.

Almost half (48%) of the women in the "19–21" age group, and one-third (35%) of the "22–24" age group did not return. This compares with 21 per cent non-returns for the "16–18," 27 per cent for the "15 or under," and 29 per cent for the "25–33" groups. Only 1 of the 9 women in the "34 and over" group failed to return for care.

A check on the relationship between living arrangements at the time of confinement and the likelihood of the patient returning for postpartum care, showed that only 40 per cent of the shelter residents returned to Mount Sinai Hospital for medical attention. The relatively best performance was shown by the group living with their parent(s) in the New York City area; 85 per cent of these women returned for postpartum care.

The review highlighted the existence of certain groups whose special problems may require close attention: The repeated pregnancy group; the under 15 years of age group; separated, widowed and divorced groups; and the therapeutic abortion group.

The Repeated Pregnancy Group

A review of the 98 multiparas, who constituted 44 per cent of the total extramarital pregnancy group, covered a number of considerations. In examining the civil status almost half (48%) were single, while 26 per cent were of the separated, widowed and divorced group who may have had the prior pregnancy in marriage, and another 26 per cent were women in consensual unions.

When ethnicity is looked at in relation to multiparity, it is found that 45 per cent of the Negro women had had a prior pregnancy, while 21 per cent of the white and 62 per cent of the Puerto Rican women had previous pregnancies. These percentages were approximately similar to those described in the Pakter study for the city (2).

In regard to their number of previous pregnancies, 36 per cent had had one prior to the current pregnancy, while the remainder ranged as follows: 23 per cent had had two, 10 per cent had had 3 and 4 respectively, while 21 per cent had had 5 or more previous pregnancies.

The Under 15 Years of Age Group

The very young unmarried mother has traditionally attracted the most attention, since the concerns are manifold. Although as a group it is statistically the smallest percentage within the total (and this is true for the City at large), the fact is that because pregnancy is not a common occurrence in this age group, out-of-wedlock pregnancies are proportionately extremely high.

In looking at the question of medical complications in this group of under 15 year-olds, although only 11 were involved, it is noted that all but one had full term normal babies with no serious physical difficulties evidenced in the prenatal and confinement periods. A recent study of 1137 pregnant adolescent girls reported "these patients presented an increase in the incidence of severe toxemia, especially in the girls of 15 years of age and under" (8). Although this was not the observation in The Mount Sinai Hospital study, the number of adolescents reviewed was too small to make any definitive conclusion.

Separated, Widowed and Divorced Group

There were 31 women who were separated, widowed or divorced and they constitute 14 per cent of the total group studied. These women were under-

standably older than other patient groups. The complications these women presented were primarily social and not medical.

Therapeutic Abortion Group

There were five patients of the total studied who had therapeutic abortions. One was Negro, 3 were white and 1 was Puerto Rican. Two of these patients had had no previous pregnancy: 2 had been pregnant once before: and 1 (the divorced patient) had had 4 previous pregnancies. One patient was aborted for medical reasons, the other 4 for psychiatric reasons. Of the latter, 3 were diagnosed as psychotic, and 1 as borderline psychotic. All 4 had had long histories of psychiatric illness and care.

A significant portion of this study concerned itself with planning for the newborn as revealed by these mothers. While two-thirds of the women planned to take care of their newborn themselves, there were marked variations by ethnic group. Adoption is the primary method of planning for the newborn by the white group. Only one Puerto Rican and one Negro woman planned adoption. This is a reflection, in part, of the relatively small demand for children for adoption by these two ethnic groups. It may also reflect the lack of agency services which would encourage or satisfy such a demand. In view of the known high rate of infertility among Negro families, and the willingness of some to undergo surgical procedures which have slight chance of correcting infertility, the data would suggest the desirability of exploring ways in which agencies could encourage adoptions, where appropriate, among this ethnic group. Physicians also might give consideration to advancing this suggestion to their Negro infertility patients.

The majority of Puerto Rican women plan for self-care of their child within a framework of consensual union, or with assistance from the public agency, while Negro women in the main take the newborn home on their own, or with the assistance of public agencies.

Hospitals and their social service departments have a special role in services to the unmarried mother not only in medical care but also in the extension of social services. Comprehensive care seems at this time somewhat more fully available to clinic and ward patients than it is to the private and semi-private patients. Private physicians as well as doctors serving in hospitals and social workers are the connecting links which can effectively put these women in touch with appropriate existing community resources. In addition, social action is essential to develop more community resources for Negro and Puerto Rican unmarried women.

The existence of the various subgroups of unmarried women emphasizes that there is no one primary method or approach which would be effective in reducing *all* out-of-wedlock pregnancies. On the contrary, the findings suggest that a special approach to each subgroup may be essential, incorporating a proper balance between individual counseling and work on a broad social front. Accordingly, follow-up studies would be appropriate to establish priorities and develop more effective techniques in medical and social services to the groups of unmarried women.

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Renal Vein Thrombosis and the Nephrotic Syndrome with Complete Remission

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Since the original description by Rayer in 1840 (1), thrombosis of the renal veins has been recognized as a rare cause of renal failure. Several reviews in recent years have stressed consideration of this disorder in the diagnosis of renal failure associated with the nephrotic syndrome (2–7). To date, approximately 300 cases have been reported, about eighty per cent of this total having occurred in children (8). In the adult, the onset is usually sudden with a fulminating course leading to death within two months. The clinical picture is characterized by oliguria, hematuria, severe flank pain, azotemia, proteinuria, and severe leg edema (9). If the patient survives the initial insult, a nephrotic syndrome may develop. In rare cases, the only symptom of occlusion is the insidious development of a nephrotic syndrome (7, 10). Survival depends upon several factors: the location and extent of the occlusion, the rapidity of its development, and the severity of any underlying renal disease. In untreated cases, unilateral thrombosis has the same mortality as bilateral thrombosis but the course may be less fulminant.

Occasional cases have appeared in which an amelioration of the symptoms was effected by nephrectomy or a combination of anticoagulant and antibiotic therapy (3, 4, 10–15).

Ten years ago a patient was admitted to the wards of The Mount Sinai Hospital with migratory thrombophlebitis and pulmonary infarction. She developed renal failure and a nephrotic syndrome subsequent to thrombosis of the inferior vena cava. Following one year of intensive antibiotic and anticoagulant therapy during which she had frequent exacerbations of her symptoms, the edema and proteinuria subsided. Since that time her renal function has been essentially normal. Her unusual and gratifying response stimulated us to survey other reported cases of renal vein thrombosis in order to determine what factors might facilitate prompt diagnosis of this disorder.

CASE REPORT

The patient is a 53 year old white female who was first admitted to The Mount Sinai Hospital on September 7, 1951 because of hemoptysis and swelling of the legs. She had been well until October 1950 when she had an acute illness characterized by transient bilateral chest pains and fever of 103°F. Her symptoms cleared spontaneously and she remained well until April 1951 when she developed fever and posterior chest pain for eight days. At the end of this period she entered another hospital because of sudden dyspnea, orthopnea, and cyanosis associated with transient symmetrical bilateral lower leg edema. This subsided without treatment and she remained well until the latter part of July 1951 when

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she again had chest pain, fever, and, for the first time, cough and hemoptysis. She was treated with antibiotics and anticoagulants. Five days prior to this first admission she developed painless swelling of the entire left leg. There had been

TABLE I

Urinalysis

Date	Sp. Gr.	React.	Prot.	WBC	RBC	Casts	Cryst.	Esbach (g./l.)
Sept. 1951	1.016	alkaline	3 plus	0	0	0	unformed	5.5
	1.010		4 plus	0	0	granular & hyaline		
Mar. 1952	1.010	acid	2 plus	10-12	0	0		1.0
Nov. 1953	1.030		slight trace	0	0	0	0	
Nov. 1955	1.010		trace	0	0	0	0	
1957			neg.	0	0	0	0	
Oct. 1958	1.019		neg.	0	0	0	0	
Oct. 1960	1.022	acid	neg.	4-5	2-3	0	0	

Hematologic

Date	Hgb	WBC × 1000	Bands	Polys	Lymphs	Eos.	Bas.	Monos.	Platelets	Sed. Rate
Sept. 1951	10.7	15.8	5	54	25	16				111
Mar. 1952	16	11.1	3	51	41	1	1	3		
Nov. 1953	13.5	6.8		normal						
Nov. 1955	14.3	9.4	2	45	45			8	25.6	7
1957	13	14							23.6	15
Oct. 1960	13	5.35		64	35				19.2	10

Chemical

Date	BUN	Creat. (mg%)	Alb. (g%)	Glob. (g%)	Chol. (mg%)	Cal (mg%)	Phos. (mg%)	Bilir. (mg%)	Alk. Ph. (K-A U)	Ceph Fl.	Th. Tur.	Pr Time (pt/c)
Sept. 1951	11		1.8	3.6								17/12
Mar. 1952	36	1.3	3.7	3.2	460	11.1						
Nov. 1953			5.0	2.4	280			3.0	39	0	.92	12/12
Nov. 1955	15		3.7	2.4	202	9.8	2.0			0		11.5/11.5
1957	13		3.9	3.3			5.5	0.8	17	1 plus		
Oct. 1960	11	1.1	3.7	2.6	220	9.1	2.6	0.4	7.1			14/12

no history of cardiac or renal disease. The remaining history and review of systems were essentially negative.

Physical examination: the patient was an alert, thin, cooperative white female in no distress. The temperature was 99.6°F, pulse 80/min. and the blood pressure 98/70 mm Hg. She had cheilosis of the lips and the tongue was reddened and smooth. In the region of the left parotid gland there was a firm, smooth, slightly movable, nontender 5 cm mass. Examination of the chest revealed dull-

ness at both bases, greater on the right side with dullness extending into the right axilla. Breath sounds were diminished at the right base. Moist rales were heard at both bases and in the right axilla. Examination of the heart was unremarkable. There was minimal distention of the jugular veins but there was no hepato-jugular reflux. The liver and spleen were not palpable. The left leg was larger than the right with pitting edema extending from the foot to the hip. The right femoral pulse was stronger than the left, but the popliteal and dorsalis pedis pulses could not be felt. Both legs were warm. There was no calf tenderness or Homan's sign. Neurological examination was unremarkable.

The results of the laboratory examination are presented in Table I.

The patient was treated with heparin, chloramphenicol and bis-hydroxycoumadin. After several days of anticoagulant therapy the hemoptysis subsided but the edema progressed to involve the entire left trunk, left shoulder and arm. On the tenth hospital day, pitting edema of the right hip was also seen. During the next five weeks the patient experienced frequent attacks of chest pain and coughing associated with low grade temperature elevations. A changing pattern of pulmonary findings suggested recurrent pulmonary embolization. During this time she was under poor anticoagulant control. At the end of the fifth week the edema subsided slightly. At this time ascites was detected. Serum albumin was 2.5 Gm%, globulin 2.4 Gm% and heavy proteinuria persisted. A chest x-ray revealed a convex density in the right lower lung field located anteriorly with fluid extending laterally. A fainter density which extended downward from the right hilum obscured the base of the lung. A thoracentesis was attempted, but no fluid was obtained. Because of the febrile course the patient was treated with penicillin and oxytetracycline and she became afebrile. Nine weeks after admission the albumin was 1.4 Gm%, globulin 3.7 Gm% but the BUN remained normal. There was continued heavy proteinuria and isosthenuria. The sedimentation rate was 111 mm/hr.

Repeat examination of the chest two weeks later revealed complete obscuration of the lower third of the right lung field by fluid. An intravenous pyelogram showed prompt excretion bilaterally with incomplete filling of the upper urinary tracts. There was no abnormality of the right kidney but on the left side the concentration of dye was insufficient to permit delineation of details. Moderate osteoporosis of the bones was noted. A repeat intravenous pyelogram taken one week later revealed prompt excretion bilaterally. No other abnormalities were found. Retrograde pyelography was normal.

During the tenth week the edema subsided considerably. At the same time, the pulmonary abnormalities cleared. Antibiotics were discontinued at the end of the tenth hospital week. Two weeks later she was taken to the operating room where a benign mixed tumor of the parotid was removed. Two days postoperatively the patient developed a paroxysmal supraventricular tachycardia which responded to carotid sinus pressure. An electrocardiogram revealed non-specific abnormalities of the T waves in the precordial leads. One week after operation the patient experienced sharp left flank pain. Her temperature rose to 102.6°F, respirations were increased to 32/min. Dullness and decreased breath sounds

were detected at the left base. There was exquisite left costovertebral angle tenderness. The chest x-ray was unchanged, as was a repeat electrocardiogram. A low grade diastolic hypertension was now present. White blood count was 14,900/mm^3. She was treated symptomatically with analgesics, oxygen and sedatives. During the next three weeks in the hospital the patient improved steadily. At this time, venous collaterals appeared over the abdomen, particularly on the left side, and the remaining edema decreased markedly. Because of the persistently low serum albumin levels she was treated with infusions of "salt-poor albumin," with subsequent elevation of her serum albumin to 4.1 Gm%, despite persistent heavy proteinuria. The serum cholesterol, which was elevated early in her course, was unchanged. The isosthenuria persisted; urea clearance was 40 ml/min. She was ambulated progressively as her edema cleared, and was discharged on the 146th hospital day free of edema and with normal serum albumin and globulin levels. There was persistent proteinuria and evidence of an extensive collateral circulation over the left side of the abdomen.

The patient was readmitted in March 1952, approximately six weeks after discharge, complaining of left flank pain of one week's duration. She had been treated at home with intramuscular heparin. Two days prior to admission the pain became more severe and marked tenderness and swelling developed over the left loin. The pain was not affected by respiration but was aggravated by positional changes. Physical examination revealed fullness and tenderness in the left loin with limitation of straight leg raising on the left. There was distention of the superficial veins of the abdomen and breasts. There was no leg edema. A distinct area of hyperesthesia was present in the left loin. The remainder of the examination was unremarkable and the laboratory data at this time are presented in Table I.

A chest x-ray revealed no evidence of recent infiltration. Two Fleischner lines were seen at the left base. Intravenous pyelography revealed prompt visualization of the opaque material with good concentration on the right side. Concentration on the left side was very poor. The lower ⅔ of the left kidney appeared broader than the right. The bones were severely demineralized, but discrete destructive lesions were not seen. A femoral venogram revealed a complete block of the inferior vena cava at the level of the midportion of the body of the 2nd lumbar vertebra. Between this level and the level of the 5th lumbar vertebra there appeared to be streak-like filling of the inferior vena cava. Within this streak-like shadow there was a group of somewhat dilated veins, presumably retroperitoneal collateral branches. A larger collateral ileolumbar vein was seen on the right. The level of complete block corresponded to the site of emptying of the renal veins. Venous pressure in the femoral veins was 25 cm of blood.

The patient was treated with a low salt, high protein diet, bed rest, heparin and testosterone propionate. The pain subsided quickly but the tenderness over the left loin area persisted until discharge. The patient remained normotensive and was discharged three weeks later subjectively improved.

She was admitted again in November 1953 because of right upper quadrant pain and jaundice for one week. Physical examination was unremarkable. There

was no right upper quadrant tenderness, liver enlargement, ascites or leg edema (Table I).

A chronically inflamed gall bladder was removed at operation. No stones were found in the common bile duct. The postoperative course was uneventful. Severe osteoporosis was again noted.

The patient was admitted for the fourth time in November 1955. During the interim she had been well except for a 10 pound weight loss and recurrent swelling of her legs for which she was treated with diuretics.

About one month prior to this admission she developed weakness and easy fatigability associated with the appearance of small purpuric spots on her legs which were present for a week at a time. New crops of purpuric spots continually appeared.

One week prior to admission she lost consciousness for 45 minutes without prodromal symptoms. No convulsive movements were seen. Physical examination showed a blood pressure of 130/70, pulse (irregular) 130/min. (apical), 86/min. (radial), temperature 100°F. The patient revealed evidence of chronic weight loss. Numerous 2 x 2 cm purpuric patches were present on the legs. A 1.5 x 1.5 cm subcutaneous hard nodule was felt on the left hip. Moderate pretibial edema was present. Neurological examination was unremarkable (Table I). A chest x-ray revealed what was considered to be a small collection of fluid or thickened pleura in the right costophrenic angle.

The patient reverted spontaneously to normal sinus rhythm shortly after admission. Electrocardiograms during and after the episode of fibrillation indicated no myocardial involvement. The patient was discharged improved, but no cause for the purpura was found.

The patient was readmitted in 1957 after two weeks of right upper quadrant pain, fever, and jaundice. Physical examination was unremarkable except for epigastric tenderness. Protein-bound iodine was 2.98 micrograms %. Several blood cultures were sterile. An LE preparation was negative. Intravenous pyelography revealed prompt excretion bilaterally. The entire urinary tract appeared normal. A gastrointestinal series was negative. Intravenous cholangiography revealed gas shadows and several defects in the common bile duct.

The patient was febrile for several days. A laparotomy and common bile duct exploration was performed and numerous small calcium phosphate stones were removed from the common duct. Following dilatation of the ampulla, a T-tube was left in place. The patient did well immediately postoperatively. She was asymptomatic throughout the remainder of this hospital admission despite the development during the first postoperative week of electrocardiographic changes characteristic of diaphragmatic wall infarction.

The patient was again admitted in October 1958 with a one week history of pain in the right leg. Physical examination was unremarkable except for a positive Homan's sign on the right. There was redness, tenderness and swelling of the right calf. She was treated with heat applications to the calf, elevation of the leg and anticoagulants. Urinalysis revealed a specific gravity of 1.019 but there was no proteinuria.

Following discharge from the hospital, the patient discontinued the anticoagulants and did well except for moderate exertional dyspnea and recurrent symptoms related to her biliary disease, until October 1960 when she was readmitted because of the sudden onset of pleuritic interscapular pain one day prior to admission. During the preceding few weeks she noticed numerous purpuric spots on her legs but no swelling or tenderness. On physical examination her blood pressure was 105/80, respiration 16/min., temperature 100°F, pulse 96/min. She was in no distress. There was no pallor or cyanosis. There was 1 plus pitting edema of the legs and the feet had a ruddy mottled color. Ecchymoses were present over the left calf, no calf tenderness was elicited and Homan's sign was negative. Funduscopic examination revealed degenerative changes of the retinae with hard exudates. The veins were tortuous, the discs flat. Examination of the chest revealed decreased vocal fremitus and inspiratory fine crackling rales over the left lateral thorax. Examination of the heart was unremarkable except for frequent premature ventricular contractions. No murmur was heard. The liver, spleen and kidneys were not palpable. No distended veins were seen over the abdomen. Neurological examination revealed decreased deep tendon reflexes, a slight left facial droop and a questionable Babinski reflex on left plantar stimulation. The left calf was 1.3 cm larger than the right in circumference (Table I).

LE preparation was negative. Bleeding and clotting time normal; clot retraction normal. Phenolsulfonphthalein 10% in 15 minutes (small sample), 45% in two hours. Creatinine clearance 45 ml/min. Examination of the blood for cold agglutinins and cryoglobulins was unrevealing. Histologic examination of a biopsy of skin, subcutaneous tissue and muscle from an ecchymotic area of the leg revealed no abnormality.

The patient was treated with bed rest, heat to the affected leg and anticoagulants. Her symptoms subsided several days after admission and she was discharged ten days later. She was advised to continue the anticoagulant treatment at home.

Initially, the patient had recurrent femoral thrombophlebitis and pulmonary embolization. The subsequent development of iliac and caval thrombosis suggested the diagnosis of "thrombophlebitis migrans." The presence of a parotid nodule and the symptoms of recurrent pulmonary consolidation led to an unrevealing search for a neoplasm as the underlying cause for the phlebitic episodes. Her course was complicated by recurrent episodes of flank pain, hemoptysis, and fever which finally responded to antibiotic and anticoagulant therapy. The development of a nephrotic syndrome and isosthenuria presumably resulted from renal vein thrombosis. This was confirmed by a femoral venogram which revealed inferior vena caval thrombosis with obstruction at the level of the renal veins. An intravenous pyelogram was suggestive of greater involvement of the left kidney. Additional evidence was provided by the development of extensive collaterals over the left trunk with coincident improvement of renal function. Treatment with intravenous albumin appeared to elevate the serum albumin concentration with concomitant clearing of the edema. The recurrent

flank pains, electrocardiographic changes, syncopal episodes, repeated chest pains and ecchymoses aroused suspicion of a generalized vascular disorder, possibly involving the arterial as well as the venous circulation. However, a skin and muscle biopsy of one of the affected areas revealed no abnormality. Hematologic studies including tests for cold agglutinins and cryoglobulins were negative. Despite the apparent persistence of her vascular disease renal function has been good since her third admission in 1953. She has been able to concentrate her urine normally, has no proteinuria, and pyelography reveals no excretory abnormalities. The only findings at present suggestive of any renal impairment are a depressed two hour phenolsulfonphthalein excretion and a reduced creatinine clearance.

TABLE II

Diseases Predisposing to Renal Vein Thrombosis

1. Amyloidosis (3, 11, 19–23)
2. Thrombophlebitis Migrans (3, 4, 6, 7, 13, 24, 25, 29, 33)
3. Congestive Heart Failure (4, 11, 26)
4. Idiopathic (3, 10, 27)
5. Metastatic Carcinoma (5)
6. Malignant Hypertension (3)
7. Glomerulonephritis (3)
8. Hypernephroma (3, 34)
9. Mercurial Diuretics (28)
10. Post-Traumatic (12)
11. Pyelonephritis (24, 26)
12. Sepsis (15)
13. Uretherolithiasis (15)
14. Essential Hypertension (12)
15. Urethral Instrumentation (15)

DISCUSSION

A differentiation in pathophysiology has been made between the neonatal and adult forms of this disorder. In the former, thrombosis is primarily intrarenal and is usually associated with dehydration and debilitation secondary to sepsis or diarrhea (6, 16, 17). The kidneys at autopsy reveal hemorrhagic infarction with extensive thrombosis of the small intrarenal vessels (18). This has been attributed to the small caliber of the neonatal renal vessels and intensification of the relative polycythemia of early infancy. Lesions of this type preclude the development of a collateral circulation. Therefore, in the untreated case, it is associated with almost certain mortality. We have not been able to find a report of a nephrotic syndrome resulting from renal vein thrombosis in the neonatal period. Cure of the condition depends upon early recognition and prompt surgical intervention. A number of reports of successful treatment by nephrectomy have appeared in the pediatric literature since the correctly diagnosed and treated cases of Campbell and Matthews in 1942 (18).

In contrast, thrombosis in the adult is usually extrarenal and in the majority of instances is due to extension of the thrombotic process from the inferior vena

TABLE III

Reference	Age/Sex	Predisposing Illness	Symptoms prior to Diagnosis	Diagnostic Measures Employed	Subsequent Course	Type of Occlusion
Shattuck 1913 (11)	30/M	Severe physical exertion. Questionable prolonged valsalva maneuver.	Lumbar pain; edema of legs, abdomen and scrotum. Proteinuria.	None.	Persistent proteinuria; superficial venous dilatation for 25 years.	Fibrosis of vena cava, renal vein thrombosis; collaterals through renal capsular, lumbar and azygos veins.
Aschner 1927 (26)	50/M	Pyelonephritis and thrombophlebitis 10 days after urethral instrumentation.	Left lumbar pain and swelling. No proteinuria.	Retrograde catheterization (anuria, left kidney).	Cured by nephrectomy.	Thrombophlebitis and thrombotic occlusion of left renal vein.
" "	36/M	Pyelonephritis secondary to urethral erolithiasis.	Pyuria, lumbar pain and swelling.		Nephrectomy.	Renal vein thrombophlebitis.
Harrison 1956 (3)	42/F	Left nephrectomy after trauma 31 years before. No other predisposing illness.	Left flank pain. Nephrotic syndrome.	Venography-thrombosis of left renal vein.	Conservative treatment. Edema subsisted. 1 Gm. prot/24 hr urine.	Left renal vein thrombosis.
" "	30/M	None.	Malaise, back pain, hemoptysis, edema and proteinuria.		Collaterals over abdomen one year later; persistent proteinuria. Died of coronary 11 years later.	Thrombosis of inferior vena cava.
" "	56/M	Cancer of lung.	Intermittent leg edema for 2½ years. Proteinuria.	Caval venography.	Deterioration and death 3 years later.	Vena caval thrombosis and obstruction.
" "	50/F	Left nephrectomy in infancy.	Dilated leg veins for 36 years. Hypertension and proteinuria for 14 years. No edema.	Caval venography.	Good response to antihypertensive drugs.	Obstruction of lower third of inferior vena cava. Narrowed renal vein.

Meriel 1959 (12)	56/M	Trauma from a fall.	Nephrotic syndrome.		Improved on symptomatic treatment. Persistent edema and proteinuria.	
Blainey 1954 (10)	34/M	No antecedent cause.	Flank pain. Nephrotic syndrome.		Nephrectomy with cure.	Unilateral renal vein thrombosis.
Pollak 1956 (4)	35/M	None.	Pleuritic pain; left loin pain several weeks later. Edema, proteinuria 3 months later.	Renal biopsy.	Heparin, antibiotics, nephrectomy (rt.). Persistent edema and proteinuria.	
Leng-Levy 1960 (15a)	45/M	Femoral thrombophlebitis.	Right loin pain and swelling; fever; nephrotic syndrome.	Caval venography.	Development of collaterals with regression of edema. 4 years later, recurrence led to death.	Vena caval thrombosis.
Austin 1961 (14)	40/F	Femoral thrombophlebitis and pulmonary embolization.	Swollen leg, chest pain and cough for 3 days; proteinuria and azotemia.	Questionable surgical venography.	Regression of symptoms on 5th hospital day. Thrombectomy.	Thrombotic occlusion of inferior vena cava. Renal veins clear.
" "	54/F	None.	Recurrent left lumbar pain, collateral circulation on left side; proteinuria, edema.	Caval venography.	Long term anticoagulation with improvement.	Thrombosis of left renal vein.
Gregg 1961 (13)	37/M	None.	Flank pain for 2 months, hypertension and albuminuria.	Intravenous and retrograde urography; surgical exploration.	Nephrectomy with cure. Thrombosis of right renal vein with proteinuria and hypertension one month later. Treated symptomatically.	Thrombosis of left, then right renal vein.

cava. A chance for survival exists if adequate collaterals can develop and if there is early recanalization (3). In occasional cases thrombosis may occur quite slowly with the concomitant development of collaterals through the renal capsule. As a result, hypertension and albuminuria may be the only symptoms (5, 13). The exception occurs in those cases of adult renal vein thrombosis secondary to intrinsic renal disease, in which thrombosis is primarily intrarenal.

A review of the literature reveals 65 cases of adult renal vein thrombosis in which sufficient clinical details were given to permit evaluation. Predisposing disorders leading to thrombosis are listed in Table II. Of these patients 63 per cent died within two months of the onset of renal failure. An additional 15 per cent were dead within two years. Although renal symptoms were usually preceded by femoral thrombophlebitis or pulmonary embolism, in many reports there was no antecedent history of these disorders. The absence of a history of phlebitis should not exclude the diagnosis of renal vein thrombosis. The development of intrarenal thrombosis was most often associated with renal amyloidosis. Characteristically, the patients developed acute renal failure superimposed on a pre-existing nephrotic syndrome, the latter presumably due to the amyloidosis. When intrarenal thrombosis was associated with other intrinsic renal diseases, the patients usually presented with a severe intensification of their pre-existing renal insufficiency. Very often this type of thrombosis was unilateral.

In patients in whom thrombosis of the renal veins was rapid and occlusion complete, a fatal hemorrhagic infarction developed. Twenty-eight per cent of the cases reviewed had little or no proteinuria prior to death. In these patients, oliguria, flank pain, hematuria, and fever were the major symptoms. In several instances, nephrectomy or thrombectomy might have been lifesaving.

Recently, several reports have emphasized the danger of renal vein thrombosis as a complication of severe heart failure (4, 11, 26), mercurial diuretics (28), and corticosteroid therapy (7). The development of severe and intractable proteinuria with hypoalbuminemia under these conditions should arouse suspicion of this diagnosis. A nephrotic syndrome has also been reported in patients with hypertensive cardiovascular disease who had superimposed vein thrombosis (3, 12). The possible confusion with the nephrotic stage of glomerulonephritis is evident.

Fourteen of the sixty-six cases studied survived for periods longer than two years, but in most of these there was persistent proteinuria or azotemia. Table III summarizes the clinical findings, course and treatment of these 14 patients. Five patients were cured by nephrectomy, and in one a thrombectomy and vena caval ligation were performed.

Despite the small number of surviving cases among those reviewed, the outlook may not be as dismal as the statistics would suggest. There may be a number of surviving cases in whom the true explanation of the renal failure was not recognized. The frequent occurrence of unilateral renal vein thrombosis in this series emphasizes the importance of early recognition and surgical intervention.

The diagnosis can usually be confirmed by one or more of the following procedures: intravenous and retrograde pyelography, renal biopsy and venography. An intravenous pyelogram may reveal poor excretion by the affected kidney and

compression of the excretory structures by the swollen parenchyma. Inability to visualize the affected kidney on the intravenous pyelogram and demonstration of compression of the renal pelvis by an enlarged kidney by retrograde pyelography is strongly suggestive of this condition. This picture has also been described as an enlarged kidney with "pseudocystic appearance" (31).

Percutaneous renal biopsy may show interstitial edema, basement membrane thickening and varying degrees of hemorrhagic infarction with preservation of the glomeruli (4, 12). It has been suggested that failure of renal biopsy to reveal the membranous glomerulitis found in the nephrotic syndrome merits consideration of a diagnosis of renal vein thrombosis (32).

Caval venography is probably the most useful procedure for the demonstration of this disorder. Varying degrees of obstruction of the inferior vena cava are readily demonstrated and the level of obstruction may be determined as well. Obstruction of a renal vein may be demonstrated by the absence of retrograde flow of the opaque material into the renal vein during a valsalva maneuver (29).

Treatment of the surviving cases was determined to a great extent by the condition of each individual patient. Unilateral nephrectomy has produced a complete cure in selected cases and the judicious use of anticoagulants and antibiotics has been beneficial in others. Cure by thrombectomy and vena caval ligation has also been described (14). In our patient, there was complete clearing of symptoms without resort to surgery. The clinical history suggests that thrombosis occurred initially in the inferior vena cava and extended to the left renal vein. Occlusion was probably incomplete. As a result, a collateral circulation developed before irreversible renal damage occurred. The disappearance of the superficial collaterals was probably associated with recanalization of the thrombosed vessels. To our knowledge, the eight year period in which this patient has remained free of renal symptoms following recovery from severe renal failure with a nephrotic syndrome is the longest complete remission thus far reported.

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Cavum Septi Pellucidi: An Illustrative Case

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Caves of the septum pellucidum ("fifth ventricle") have been appreciated since the seventeenth century. They were known to Jacobus Sylvius, the French anatomist. The first written description is attributed to Ferrario; however, an Italian anatomist, Andrea Verga, in his letter to Ferrario, claimed priority of description on the basis of his anatomic notes. The space immediately posterior, the cavum vergae ("sixth ventricle") bears his name.

The corpus callosum defines the anterior, posterior, and superior limits of the fifth and sixth ventricles. The cavum septi pellucidi is bordered anteriorly by the genu of the corpus callosum, posteriorly by the anterior limb of the fornix, superiorly by the body of the corpus callosum, inferiorly by the rostrum of the corpus callosum, and laterally by the layers of the septum lucidum. The cavum vergae is bordered anteriorly by the anterior limb of the fornix, posteriorly by the splenium of the corpus, superiorly by the body of the corpus callosum, and inferiorly by the psalterium and hippocampal commissure.

When the walls of these structures are intact, they are known as cysts; when in communication with the ventricular system they are known as caves. Reports of cases have been contributed by Meyer (1), Dandy (2), VanWagenen and Aird (3), Pendergrass and Hodes (4), Love, Camp, and Eaton (5), Lowman, Shapiro, and Collins (6), Berkwitz (7), Echternacht and Campbell (8), Miller (9), Wolf and Bamford (10), Silberman (11), Olsen (12), and Hughes, Kernohan, and Craig (13). Craig, Miller, and Holman (14), in an interesting article, reported cysts of the cavum pellucidum occurring in twins. The cysts ruptured following pneumoencephalography, thus rendering surgical treatment unnecessary.

The following case illustrates the well-defined roentgenographic findings as well as the complex clinical picture.

CASE REPORT

The patient, a 19 year old, right-handed male, was admitted to The Mount Sinai Hospital on September 25, 1961 because of weakness of the left extremities of one week's duration.

The child was the product of a normal gestation. He began to talk at the age of 18 months but had to "relearn to talk" after a tonsillectomy at age two. His speech was always slurred despite speech training and the services of an orthodontist. He completed the seventh grade at the age of 18.

One year prior to admission he was hospitalized because of paranoid ideation, suicidal thoughts, and visual hallucinations. He was treated with phenothiazine drugs and shock therapy. Episodes of shaking of the left extremities and urinary incontinence had occurred.

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One week prior to admission, while on his way to work as a delivery boy, he noted increase in speech slurring and weakness of the left extremities. Bifrontal headache occurred. These symptoms waxed and waned. There was no diplopia, blurring of vision, or nuchal rigidity. He was admitted to the hospital for further evaluation.

Physical examination revealed a well-nourished young man who was in no acute distress. The vital signs were within normal limits. Multiple skin lesions (papules, pustules, and comedones) were present on the face and trunk; adenoma sebaceum was not present.

The neurological examination found the patient to be oriented to person and

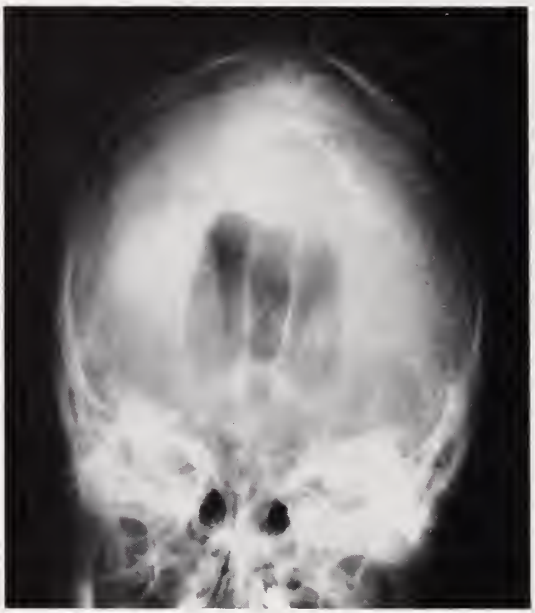

FIG. 1. Cave of the Septum Pellucidum. The brow-up Towne film reveals the midline cave of the septum pellucidum to be as large as the lateral ventricles.

place but not to the exact date. His fund of general information was adequate; there was no specific dysphasia. He laughed frequently. His gait was disturbed by a limp favoring the left lower extremity; tandem gait was poor; the Romberg sign was positive. Left hemiparesis (strength approximately 25% normal) was present. Left facial weakness and deviation of the tongue to the left were noted. Speech was dysarthric. There was generalized hyper-reflexia (left greater than right), bilateral Babinski signs, and diminished superficial abdominal reflexes. Palmomental reflexes were present bilaterally. There was no sensory or visual field defect.

The routine blood and urine studies were normal. The fasting blood sugar was 80 mg per cent. The serum calcium was 10.7 mg per cent and the serum phosphorus 3.3 mg per cent. The spinal fluid protein was 18 mg per cent; Wassermann negative; colloidal gold curve, 1111100000. The plain skull films were unre-

markable as was a right carotid arteriogram. The electroencephalogram was abnormal and revealed evidence of left temporal region dysfunction. There were isolated spikes and sharp waves from this region along with less frequent bursts of irregular 2–5 cycle per second slow waves with amplitudes up to 150 microvolts.

The pneumoencephalogram was remarkable in that a large cave of the septum pellucidum was present. In the brow-up films (Figs. 1, 2) the cave was equal in size to that of the lateral ventricles. Other views demonstrated that a cavum vergae as well as a cavum septi pellucidi was present. These structures were in continuity with each other. The suprapineal recess was particularly prominent

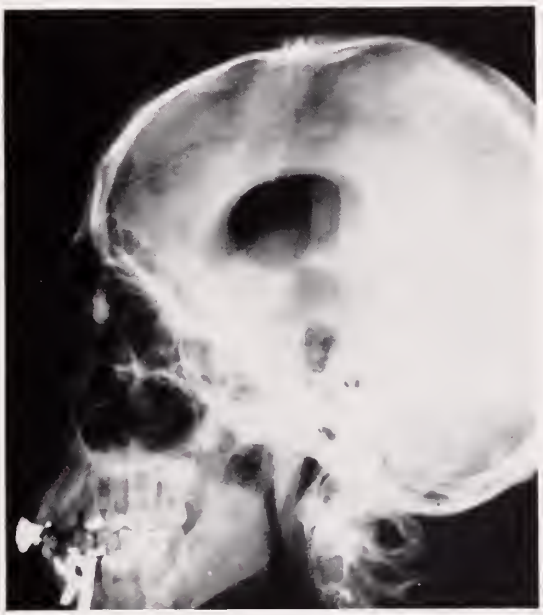

Fig. 2. Cave of the Septum Pellucidum. Brow-up lateral film.

and appeared to communicate with the cavum vergae. There was slight enlargement of the entire ventricular system but no evidence of displacement.

During hospitalization fluctuations in the intensity of the left hemiparesis were noted. Frontal headache, vomiting, incontinence, and twitching of the left lower extremity occurred and gradually subsided. The patient was discharged, essentially unchanged, after two weeks of hospitalization. Follow-up communication in August 1962 revealed that the patient had worked at several jobs for brief periods. There had been little change in his physical condition.

The literature contains a number of reports of cysts and caves of the septum pellucidum. In certain of these cases the patients were asymptomatic and the diagnosis was made by pathological examination. In other cases the abnormality was associated with tumor of the hemisphere or midbrain. There appear in the literature, however, 28 cases in which cysts or caves of the septum pellucidum were symptomatic and in which an adequate clinical history was recorded. Using

these cases and the one herein recorded, we are able to tabulate the frequency of signs and symptoms associated with this condition. The 29 cases were not associated with tumor or other significant pathology.

The ages of the 29 patients in this group ranged from 5 months to 52 years. Clinical findings were noted as follow: mental changes, 16; headache, 15; seizures, 15; reflex changes, 13; motor weakness, 10; unconsciousness, 9; ataxia, 9; visual deficit (blurring of vision, diplopia, or field defect), 8; cranial nerve dysfunction, 6; speech disorder, 5; tinnitus or deafness, 4; nystagmus, 4; papilledema, 4; sensory changes, 3.

It is apparent that the clinical findings associated with cysts or caves of the septum pellucidum are not diagnostic. Encephalography is necessary for evaluation. However, certain findings, although recorded only occasionally, warrant comment. Intermittency of headache, often severe, has been mentioned in two cases. Dandy studied the case of a 50 year old woman who had severe, recurring, generalized headaches eleven years prior to her admission. The headaches had disappeared five years before admission (2). Ventriculography revealed a large cyst of the septum pellucidum. VanWagenen and Aird (3) reported the case of a 43 year old male who suffered from headache after a fall from a roof eight months previously. The past history was remarkable in that the patient had childhood bouts of headache which ended abruptly at the age of 13, after a particularly severe attack. An encephalogram revealed a small dilatation of the cavity of the septum pellucidum. Headache stopped almost completely following this procedure. The authors speculated that the cessation of the headaches at the age of 13 may have been due to a rupture of such a cyst.

The seizures reported in association with this disorder are not always typical. In the second case reported by Dandy (a 4½ year old boy) the following description was recorded, "Left sided convulsions were frequent but without the 'Jacksonian march' (2). In fact, the convulsions were of a variable character. Occasionally both legs and one (either) arm would jerk. There was at times flaccid paralysis of the entire left side; at other times only the left arm was said to have been paralyzed."

VanWagenen and Aird describe the pattern in a 39 year old male as follows, "During an attack the head was held extended and the arms and legs were very stiff and rigid, with coarse tremors of the muscles. Tonic and clonic movements did not occur" (3). In our case somewhat characteristic twitching of the left lower extremity occurred during hospitaliaztion.

SUMMARY

An illustrative case of cavum septi pellucidi is presented. The symptomatology of 29 cases is analyzed. Mention is made of intermittent headache and atypical seizures. While the clinical picture is not diagnostic, the encephalographic findings are distinctive.

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CLINICO-PATHOLOGICAL CONFERENCE

Fever, Anemia, Leukocytosis, Blindness and Hemiparesis

Edited by

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A 62 year old, retired, American-born businessman was admitted to The Mount Sinai Hospital complaining of blindness in the right eye for four days and left hemiparesis for one day.

The patient had been well until the last six weeks when he noted fatigue, calf soreness, and ankle edema. He was found to have anemia and a white blood count of 18,000/mm^3. The bone marrow was hypercellular with a moderate increase in promyelocytes and myelocytes. The sedimentation rate was 140 mm/hr and the prothrombin time, serum proteins, protein electrophoresis and cephalin flocculation were normal. The spleen was enlarged but regressed after treatment with 6-mercaptopurine and 6 blood transfusions. The number of myelocytes decreased in the marrow but the platelet count fell to 80,000 and the anemia persisted. He had a fever spike after each transfusion. He had nosebleeds for three weeks but no other bleeding. Because the fever spiking up to 104° following the last transfusion had not abated in three days, he was admitted to the hospital. On examination his temperature was 99°. Other vital signs were normal. Fresh flame hemorrhages were seen in the retina of the left eye. Occasional rales were heard at the right base. A grade II basal systolic murmur was noted. The liver edge was down 2 fingerbreadths but no spleen was felt. Scattered petechiae were present on the legs. The urine contained 1+ albumin but was otherwise normal. Hemoglobin was 7.7 Gm%, hematocrit 23%, red cell count 2.39 million, reticulocytes less than 0.5%, platelets 20,000/mm^3, white blood cells 1,400/mm^3 with 51% segmented leukocytes, 36% band forms and 13% lymphocytes. Stool guaiac examination was 4+, BUN and uric acid were normal. The blood sugar was 192 mg% and serum alkaline phosphatase was 31.7 King Armstrong units. Blood culture showed no growth. Chest x-ray, intravenous pyelogram and visualized bones, barium enema and upper gastrointestinal series were normal. The gallbladder which filled well had multiple nonopaque calculi. The right paranasal sinuses, particularly the antrum, were cloudy. The patient continued to have temperature spikes despite short courses of chloramphenicol, tetracycline and Cytoxan. Prednisone was started in doses of 125 mg a day and the temperature promptly fell to normal and remained there. After four weeks in the hospital and two weeks of steroid therapy, the hemoglobin was 12 Gm%, hematocrit 36%, red blood count 4.25 million, reticulocytes 1.6%, platelets 178,000, white blood count 3,450/mm^3 with 34% segmented leukocytes, 23% band forms, 2% myelocytes, 21% lymphocytes and

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20% monocytes. The blood sugar levels and the serum alkaline phosphatase returned to normal. Aside from localized right-sided headaches, the patient felt well and was discharged on methyl prednisilone 50 mg daily.

During the first week that the patient was at home, a large amount of pus drained from his right axillary antrum. Following this, right retrobulbar headaches became very severe. Blurred vision and photophobia were noted in the right eye and diplopia occurred occasionally. He was afebrile until he had been home twelve days at which time his temperature rose suddenly to 105°. The white blood count and platelet count were normal. He was readmitted to the hospital with a temperature of 100.4° and a regular pulse of 104/min. The right nasal passage was filled with inspissated and crusted material. The right palpebral fissure was widened and the right eye was protuberant, tense and tender. The pupils and eye grounds were normal. The heart and lungs were normal. The liver edge was down 5 fingerbreadths, the spleen tip 2 fingerbreadths. Neurological examination was normal except for slight left ankle paresis. The urine contained a trace of albumin, a few red and white cells and an occasional granular cast. Hemoglobin was 12.9 Gm%, hematocrit 40%, red blood count 5.2 million/mm^3, platelet count 190,000/mm^3, white blood count 8,350/mm^3 with 46% segmented leukocytes, 30% band forms, 16% lymphocytes and 8% monocytes. BUN and serum electrolytes were normal. Spinal fluid dynamics, protein and sugar were normal and no cells were present; cultures showed no growth. LE preparations and urine cultures for acid fast bacilli were negative. Chest x-ray was normal. The paranasal sinuses were clearer than previously. The skull and lumbar spine were normal. Despite continued methyl prednisilone and x-ray therapy to the right orbital area, right proptosis with right abduction palsy and diplopia, and the left ankle drop became worse. Temperature elevation to 101° also continued. After 17 days in the hospital he was sent home to continue on steroids.

At home his condition was unchanged for 25 days. Then his right eye became blind and hearing diminished in the left ear. Headache and lethargy were prominent. The following day pains developed in and around the left eye. Temperatures rose to over 104° at least twice a day. Two days after the onset of the blindness he could not walk unaided and on the day of the final admission left facial weakness and then general left hemiparesis became apparent. The physical findings were the same as on the previous admission except for more severe left-sided weakness worse in the leg than in the arm. The right optic disc showed no cupping. Pulsations of the vessels of the right fundus were questionably less than those of the left. Hearing on the right was diminished. There was some sensory deficit in the right lower extremity. The hemoglobin was 11.6 Gm%, white blood count 7,100/mm^3 with 70% segmented leukocytes, 20% band forms, 6% lymphocytes, 2% monocytes and 2% eosinophiles. The urine contained 2+ albumin and a few white cells. BUN was 13 mg%, blood sugar 356 mg%, serum calcium 8.5 mg%, phosphorus 1.7 mg%, alkaline phosphatase 9.4 King Armstrong units. The sedimentation rate was 104 mm/hr. Blood and spinal fluid cultures and serology were negative. Spinal fluid protein was 172 mg%, sugar

97 mg% and chlorides 115 mEq/L. Pressures were normal and the cell count was 61/mm^3 with 55% segmented leukocytes and 6% lymphocytes. LE preparations were negative. Serum electrolytes were normal and two repeated blood sugars were over 200 mg% while one was normal. X-rays of the optic foramina and skull were normal. Right carotid arteriography was difficult to interpret because of some apparent intramural injection of the wall of the vessel. No one level of obstruction could be visualized but the vessel did not fill well. Left carotid arteriography was normal except for some segmental beading near the sella turcica. EEG indicated diffuse cerebral dysfunction without specific localizing or diagnostic significance.

In addition to the steroids the patient was given penicillin and chloramphenicol. Fever up to 104° continued. On the third hospital day the patient had a 45 minute episode of aphasia and twitching. On the fifth hospital day he was apathetic with twitchings around the right eye. The right side of the face was swollen and the left hemiparesis was worse. At this time ophthalmodynamometry revealed a pressure of 50/15 in the right eye and 110/70 in the left. On the sixth day he became stuporous although he continued to respond to touch and pinprick in all four extremities. Both corneal reflexes were present but the right pupil was dilated and fixed. Temperature rose to over 105° and the following morning the patient expired.

Dr. Solomon Estren:* I have to begin with the patient's final illness and try to work backwards from it. The features of the final illness are 1) aggressive course despite all therapy, characterized by fever, anemia, leukocytes, hepatosplenomegaly; plus 2) some kind of localized involvement at the right orbit (that is, a second group of signs); plus 3) something going on in the right hemisphere (a third group of signs).

The original thought was that if all three groups represented a disease involving several parts of the body including the bloodstream, it had to be lymphosarcoma of some sort. It is difficult to establish a diagnosis of lymphosarcoma in this patient. He had hepatomegaly, splenomegaly and fever but he never had lymphadenopathy and his chest x-rays were normal. The patient had certain changes in the peripheral blood which were interpreted as leukemia but these were not found later. The progressive deterioration of the right eye could be explained by a lymphosarcoma in the orbit pushing the eye out, thus causing the diplopia and other features, and with subsequent involvement of the right hemisphere. But when lymphosarcoma and leukemia involve the central nervous system, they do not involve the parenchyma by infiltration, but rather the meninges. When they do affect the central nervous system, generally they do so as a result of bleeding secondary to thrombocytopenia. In a series of cases of leukemia in which the central nervous system was involved, about sixty per cent of the involvement was due to hemorrhage in the brain as a terminal event.

Although lymphosarcoma would tie these three groups of signs and symptoms very neatly together, we have no confirmatory evidence for it. The fact that the eye did not improve after radiotherapy is a small point against lympho-

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sarcoma of the orbit. The fact that the patient was given 6-mercaptopurine and improved would go along with a leukemia rather than lymphosarcoma. It is a fact that with all this involvement there was nothing that could be biopsied successfully. Specifically there were no enlarged nodes. The absence of nodes in the mediastinum does not rule out lymphosarcoma but perhaps it is another small point against it.

I think it would be wiser to put lymphosarcoma aside for a moment and consider the possibility that at least part of the patient's terminal illness is easily explained. This man had sinusitis. If he had antral sinusitis, he very likely had pansinusitis. If pus was drained from the right antrum, in all likelihood he had some in the right ethmoid and right frontal sinuses. All these are around the eye. That he did not respond to x-ray therapy may be a small point in favor of an infection in the sinuses with pus spreading up into the floor of the orbit, continuing behind the eye, producing retrobulbar pressure and ultimately causing blindness.

It is possible for the infection to have spread further in the direction of the temporal lobe, causing a left facial and left hemiparesis, or to have induced thrombosis of some blood vessels, and in this way comprising certain areas of the brain. I am told that cavernous sinus thrombosis would produce a much more dramatic picture of the eye than is described here. An abscess, for example in the frontal sinus, may spread through the roof of the orbit and then spread up toward the temporal lobe on the right and cause no involvement clinically until a left hemiparesis and a left facial palsy develop. A second possibility is that he had a sinus abscess, retrobulbar abscess and an abscess of the brain.

This man had a hepatosplenomegaly, and on that basis alone we should seriously consider the possibility of one of the lymphomatous diseases. Death in lymphoma, if nothing else happens to the patient, is characteristically either by infection or by hemorrhage. It is possible that this patient's 45 minute episode of aphasia and twitching on the third day, apathy and twitching around the eye on the fifth day, and progressive downhill course with death on the seventh day was the result of a hemorrhage in the right temporal lobe of the brain.

Was he entitled to leakage on the basis of his blood findings? At this particular time he had no hemorrhagic diathesis. Although it is true that leukemia and lymphomas may occur without an overt hemorrhagic diathesis, it would be difficult to justify a diagnosis of cerebral hemorrhage in its absence even if one wanted to accept the diagnosis of lymphoma.

I think that the best clinical diagnosis that I can make at the present time is some sort of a malignant lymphoma plus a pyogenic infection surrounding the right eye with extension to cause involvement of the right side of the brain. I cannot make a diagnosis of leukemia although leukemia may have been successfully treated.

Dr. Charles M. Newman:* The x-ray film of the chest was normal. There were no infiltrations in the lung and no involvement of the mediastinum.

The maxillary antrum showed a very marked clouding on the right. I am not

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surprised that they found it full of pus. You can see the difference between the antra on both sides. The antrum on the right side is cloudy.

In the view of the skull, much greater density was seen on the right side through the right orbit than on the left, but we are told in the protocol that there was a proptosis, and this could be the cause of that. I do not see any evidence of any regional erosion of the sphenoid ridges or the greater or lesser wings. The orbital fissures are symmetrical on both sides without evidence of destruction.

The protocol says that the optic foramina were normal on both sides. I do not think that they are. On the left side a good optic foramen was seen which was smooth and its walls were seen well. They were not sclerotic and not destroyed. However, on the opposite side the optic foramen was much larger and the walls were irregular. The inferior wall was almost gone completely. The superior wall was also thin but relatively intact. This usually indicates that there was some mass in the vicinity of the optic nerve which was going through that foramen. It could be a little medial or a little lateral, something in the region of the optic chiasm.

Dr. Estren: Was it a neoplasm?

Dr. Newman: I have never seen this occur with infection. This does not look like localized osteomyelitis but it does not necessarily mean neoplasm.

On the arteriogram of the right side, I think we learned something more in a negative way than in a positive one in this case.

A small amount of the contrast material was seen early extending upward in the vicinity of the internal carotid and it came more or less to a point. This is not the type of picture seen with an obstructing lesion, a thrombus or a large atherosclerotic plaque in the internal carotid. Some of the external carotid branches filled. Ordinarily with an obstructing lesion of the internal carotid, some filling of the ophthalmic artery and perhaps some retrograde filling of the carotid siphon and perhaps even filling of the internal vessels occur. In the second arterial phase, the area of the point was seen and no filling of the ophthalmic artery but considerable filling of the vertebral artery. On the right side, when there is some form of obstruction, retrograde filling downward and up the vertebral artery occurs. There was some filling of the basal artery and some filling of the posterior cerebral, middle cerebral, and a small amount of the anterior cerebral arteries. We saw dye in the carotid siphon, but the chances are the carotid siphon was being filled by the posterior communicating artery rather than the ophthalmic artery.

This indicated a block but not the type with a thrombotic lesion. I do not know the condition of this vessel but I do know that there was no large space occupying lesion in the vicinity of the carotid siphon.

I think that we get even more information from the filling on the opposite side. The internal carotid at the bifurcation was clean and smooth. Both anterior cerebrals filled as did the left middle and posterior cerebral arteries. We saw no filling of the vertebral or posterior circulation.

We found, on frontal projections, filling of the carotid siphon, of the middle

cerebral artery, and of both anterior cerebral arteries. The horizontal portion of the anterior cerebral artery on the right side, although the left side was injected, showed retrograde compression, which was a little higher than on the left side. I do not believe it was enough to make a definite statement that there was any mass inferior to it. The middle cerebral artery was not grossly displaced on either side nor were either of the anterior cerebral arteries displaced.

Unfortunately we did not get enough filling downward of the carotid siphon on the right side.

Dr. Pedro Pasik:* In neurology we use ophthalmodynamometric tests to help in the diagnosis of carotid arterial occlusion. In a case of blindness of one eye and possibly involvement of the cerebral hemisphere of the same side, we might suspect carotid arterial occlusion on that side. In this case there were many other things such as proptosis of the right eye. The readings were low compared with the opposite side.

Dr. Emanuel Rubin†: In this man, who may have lymphoma or leukemia, who may also be diabetic and who has sinusitis and proptosis, did you entertain the diagnosis of mucormycosis? This disease causes thrombosis of the vessels and very often involves the sinuses. It is often reported in patients with leukemia or lymphomas, diabetes and sometimes in patients with tuberculosis. The diagnosis can only be made by a finding in tissues.

Dr. Frederick G. Zak‡: You have to think of it, put material into appropriate culture media, and ask the technician specifically to identify fungi. Otherwise the culture will be discarded as a contaminating mold.

I will begin backwards and first elucidate the mechanism of this man's death and then the generalized disease which in some ways is connected with his demise as well.

At the time of autopsy when the brain was removed, an extensive subarachnoid hemorrhage was seen fairly symmetrically distributed and mainly on the base of the brain (Fig. 1). The area of the optic chiasm was also covered with this seemingly purely bloody extravasation. We did a series of frontal sections to show the damage done by the hemorrhage. The lateral ventricles were somewhat dilated but free of blood. A section further back showed an extension of the hemorrhage at the base of the brain into the peduncle. In sections through the midbrain and the pons, there was blood in the ventricular lumen as well as blood on the outside. In sections through the medulla oblongata at various levels, the fourth ventricle was found to contain blood. We have to assume that the hemorrhage most likely took place into the ventricular lumen seeping to the basal cisterns.

In addition to the fresh blood in the subarachnoid space, there was a distinct polymorphonuclear exudate of a meningitic nature, which tallies with clinical findings of increased numbers of leukocytes in his spinal fluid. Veins were seen surrounded by lymphocytes rather than polymorphonuclear leukocytes, point-

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ing perhaps to an older process of meningeal inflammation, which was more obscure. Similar vessels were seen in sections of the spinal cord and even in some of the roots. There was no question that we were dealing with a suppurative meningitis.

The circle of Willis was removed in toto (Fig. 2). Where the right internal carotid entered, there was a ruptured, partly occluded aneurysm which was closely attached to the right optic nerve. Microscopically, a suppurative process was noted inside and outside the aneurysmal vessel wall. This was also seen in the right middle and anterior cerebral arteries (Fig. 3). Special stains brought

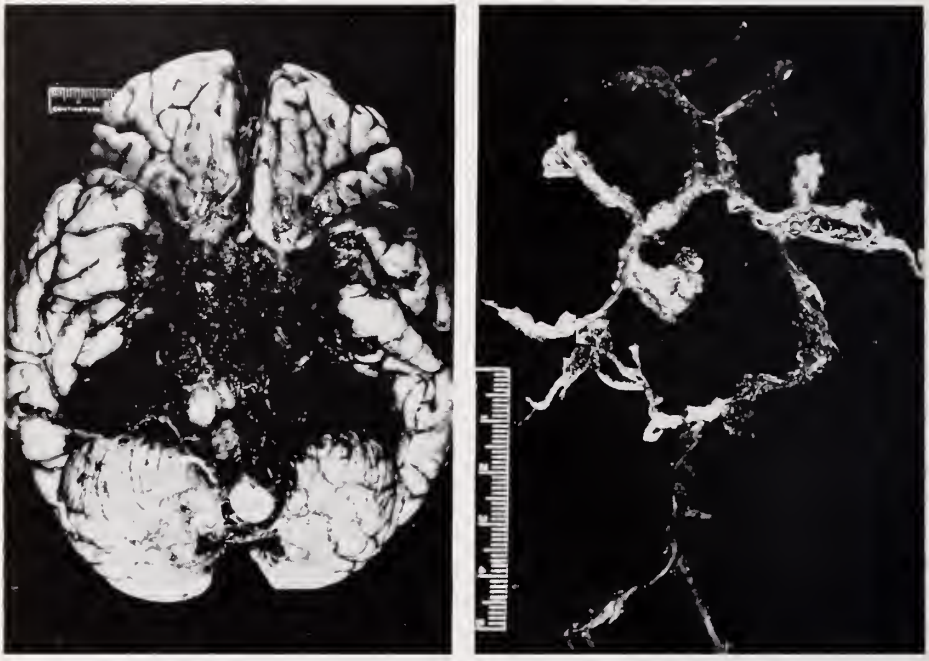

Fig. 1. Fresh subarachnoid hemorrhage at base of brain.
Fig. 2. Ruptured aneurysm of right internal carotid artery appearing as a club-shaped structure within the circle of Willis.

out innumerable gram-negative rods. We were therefore dealing with a pyogenic organism, which produced a suppurative arteritis.

Pallor was noted in the right optic nerve which was due both to the pressure that the aneurysm exerted and also to the subsequent purulent inflammation within the nerve (Fig. 4).

At the time of the autopsy, the neuropathologists opened the sphenoid sinus, which is the most readily accessible, and found it filled with pus. It grew out staphylococcus aureus and B. pyocyaneus which was apparently the main invader. Therefore, we were confronted with a pyogenic process, as Dr. Estren postulated, which perhaps was aided and abetted by the drainage. You will recall that shortly after the antrum was drained, the patient's symptomatology

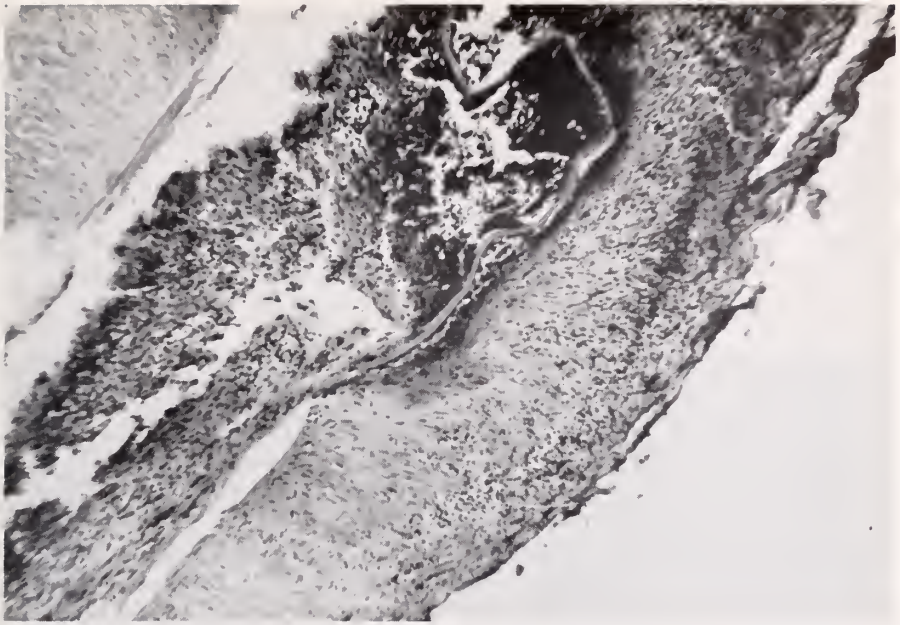

FIG. 3. Acute suppurative pyocyaneus inflammation of right anterior cerebral artery.

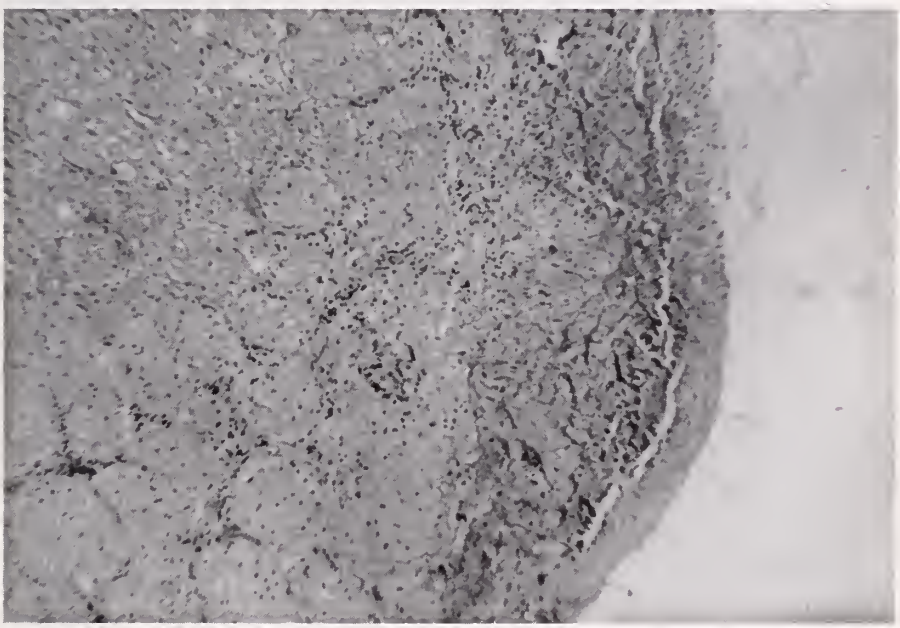

FIG. 4. Acute right optic neuritis.

became more florid. In addition the cytostatic agents which he received and the steroids may have helped the intracranial spread of the infection.

In the liver which weighed 1,500 grams, we noticed small yellow nodules surrounded by areas of atrophy. Microscopically they looked like rather acellular areas of necrosis with a sprinkling of cells. Larger lesions which were more advanced were also seen.

In the spleen which weighed 350 grams, these areas, somewhat dry and grayish yellow, were present and some were several millimeters in diameter. At first glance they had a resemblance to fibrin but further study showed this to be a peculiar areactive type of necrosis.

Fig. 5. Caseous and gelatinous tuberculous pneumonia.

In the cortex of the kidney, again a few grayish nodules were seen. Here we found infiltrates which appeared more cellular than those that we saw in the liver and spleen. These could now be studied with greater advantage microscopically and the cells were masses of epithelioid cells surrounded by a little ring of lymphocytes. This was diagnostic of tuberculosis.

In the bone marrow typical miliary tubercles accompanied by Langhans' giant cells were noted.

Both lungs were x-rayed, looking for a calcified primary focus, but were negative. The tracheal bifurcation and the accompanying lymph nodes likewise did not show calcific foci on x-ray. We have to assume that this tuberculosis was not an old infection or a reactivation but apparently a very recent infection.

We went back to the lung and took additional sections, and found in the

upper lobe an area not larger than 1½ cm which showed a little bit of pigment in the center. This is presumably the oldest lesion that he had. This was a fairly acute, tuberculous, caseous and gelatinous pneumonia (Fig. 5). The epithelioid cells were already undergoing necrosis filling the alveoli. On silver stain, some new fibers were seen to be laid down. In other areas, however, under lower power, the rim of the process had quickly undergone caseation necrosis (Fig. 6) as would be expected in a person who received cytostatic drugs instead of antituberculous drugs. Here and there in the lung sections we found single tubercles mainly composed of epithelioid cells.

We are quite certain that the patient had tuberculosis. We saw only occasional

Fig. 6. Caseous tuberculous pneumonia. H & E × 40.

giant cells but this is characteristic of this form of tuberculosis. With special stains, we were able to see the tubercle bacilli (Fig. 7) although cultures had become contaminated. We could not tell whether it was human strain or bovine, as it occasionally occurs, because a culture was not available.

The bloodstream invasion came from massive lymphatic involvement. There was extensive caseation in the paratracheal (Fig. 8), supraclavicular, mediastinal, mesenteric, portal and pancreatic lymph nodes. These provided us with the diagnosis of a peculiar form of acute tuberculosis, which is reported in the literature as generalized caseous tuberculosis of the lymphatico-hemopoietic system (1) or, as we prefer to call it, of the lymphoreticular system. This condition is classically accompanied by a leukemoid reaction.

Dr. Estren: This is the third or fourth time in two years that we of the Department of Hematology have been stung in the identical way. Given a patient

who looks as if he has leukemia, but with something peculiar about the leukemia, one should think of tuberculosis. We feel so strongly about this possibility that some of us have treated patients with these bizarre forms of what might be leukemia with anti-tuberculous drugs, but without effect. It is an important differential which we have to bear in mind in these patients with what turns

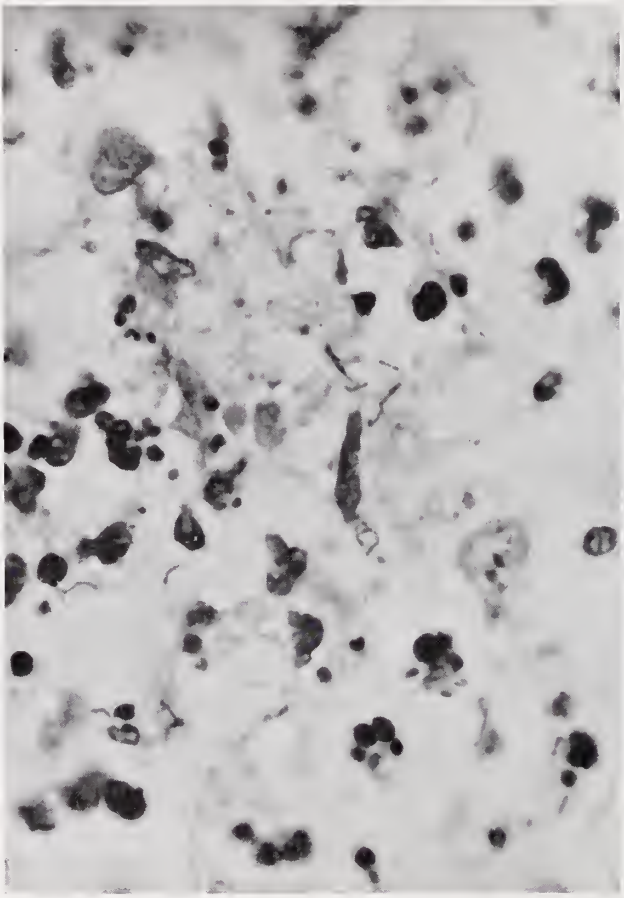

Fig. 7. Tubercle bacilli stained with Night Blue oil immersion. × 950.

out to be a leukemoid reaction rather than frank, easily diagnosable leukemia.

Dr. Zak: I do not know whether this form of tuberculosis really is amenable to anti-tuberculous therapy. My experience with these cases goes back to the era before specific therapy was introduced. These cases are rare. I want to stress that this is not a true miliary tuberculosis, but generalized caseous tuberculosis of the lymphoreticular system. Clinically, it is a very hard diagnosis to make. One does not see tubercles in the eyegrounds. It is difficult to find them in the sternal marrow, although it is possible. The urine can be cultured but this is a slow procedure, so one would have to treat the patient as if he had tuberculosis.

I have seen cases where the tuberculosis involved superficial nodes as well. An axillary node could be removed and would provide the diagnosis.

Dr. Estren: How long had this been present before death?

Dr. Zak: The findings correspond very nicely with the six week history prior to his admission.

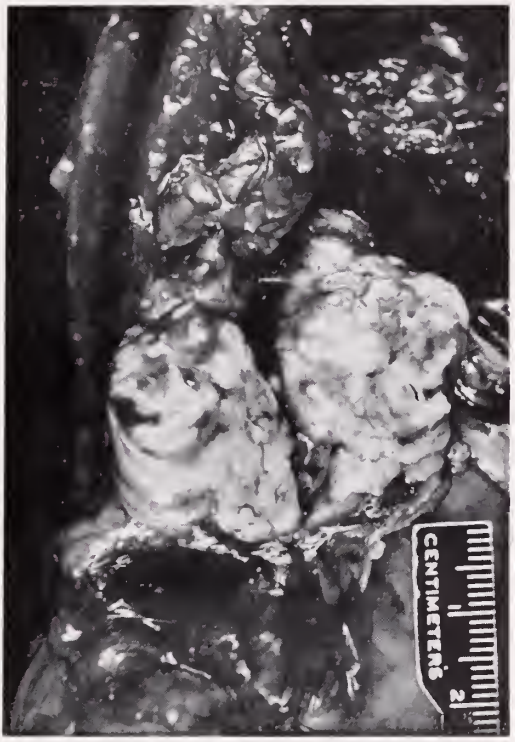

FIG. 8. Massive caseous tuberculosis of paratracheal lymph nodes.

Final diagnosis:

1. SUPPURATIVE RIGHT PARANASAL SINUSITIS WITH EXTENSION TO RIGHT OPTIC NERVE, MENINGES AND BRANCHES OF RIGHT INTERNAL CAROTID ARTERY;

2. RUPTURED ANEURYSM OF RIGHT INTERNAL CAROTID ARTERY, POSSIBLY DUE TO SEPTIC ARTERITIS;

3. INTRAVENTRICULAR AND SUBARACHNOID HEMORRHAGE;

4. MENINGITIS SECONDARY TO SUPPURATIVE SINUSITIS WITH SEPTIC OPTIC NEURITIS;

5. CASEOUS LYMPHORETICULAR TUBERCULOSIS INVOLVING LYMPH NODES, SPLEEN, LIVER, KIDNEY AND LUNGS, WITH TERMINAL MILIARY SPREAD AND LEUKEMOID REACTION.

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RADIOLOGICAL NOTES

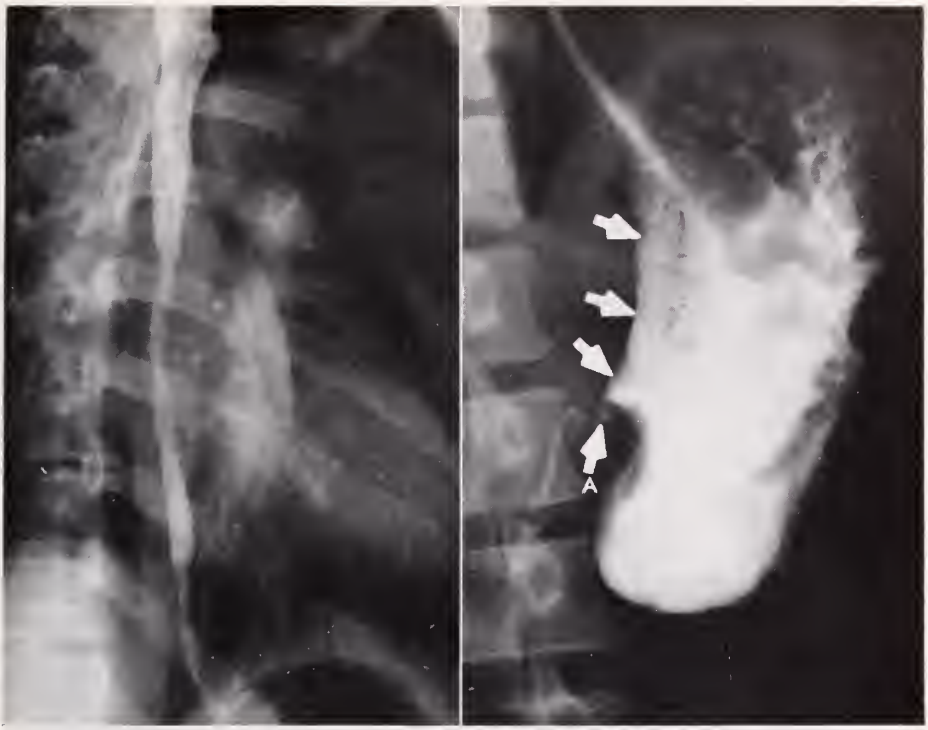
CLAUDE BLOCH, M.D., AND HARVEY M. PECK, M.D., Co-Editors
New York, N.Y.

CASE NO. 192

One week prior to her present hospitalization a 29 year old woman swallowed a large glassful of concentrated lye. At another hospital, the patient underwent esophagoscopy the day following the lye ingestion at which time severe mucosal congestion and superficial ulcerations were seen. Esophageal dilatation by bougies was then performed daily under general anesthesia because of severe dysphagia. At the time of the present admission, examination of the patient revealed markedly necrotic areas measuring 1 cm in diameter on the lips, soft palate and oropharynx. Indirect laryngoscopy revealed extensive confluent ulcerations and exudate formation involving the uvula, epiglottis, valleculae and aryepiglottic folds. The patient was placed on antibiotics, intravenous feedings and corticosteroid therapy. Esophagoscopy and dilatation were resumed at biweekly intervals because of the periodic recurrence of severe dysphagia. Three weeks after the lye ingestion, esophagoscopy showed a thick exudate covering the mucous membrane of the entire esophagus. The lower third of the esophagus was considerably contracted with a lumen of 3 to 4 mm diameter. During the fourth week of her hospitalization, the patient had clinical evidence of gastric obstruction. Barium meal examination was then performed. This revealed a concentric narrowing involving the entire length of the thoracic esophagus (Fig. 1). There was no evidence of discrete mucosal ulcers or associated mass lesions within the esophagus. Fluoroscopically, the esophagus was noted to be markedly irritable and there was severe restriction of distensibility of its walls. The barium entered the stomach promptly. Within the slightly dilated stomach moderately increased secretions were seen. The lesser curvature of the stomach was markedly shortened and appeared rigid (Fig. 2). There was a constant area of marked narrowing of the antrum near the recentrant angle. The edges of this stenotic segment were smooth and the mucosal pattern outlined within it appeared normal. A small amount of barium passed through this strictured segment and outlined the distal portion of the antrum and pylorus. The visualized mucosa also appeared intact. There was almost total retention of the barium mixture within the stomach at the end of four hours. The patient was treated with Levin tube suction but because of the lack of response to this form of therapy, gastrojejunostomy and subtotal gastric resection were performed to relieve the obstruction. In the postoperative period, frequent esophagoscopies and dilatation were required to control the dysphagia. At the time of her discharge, the patient was able to maintain her nutritional status easily by oral feedings.

Case Report: LYE STRICTURE OF THE ESOPHAGUS AND ANTRUM OF THE STOMACH.

From the Department of Radiology, The Mount Sinai Hospital, New York, N.Y.



Case 192, Fig. 1. Barium meal examination reveals a concentric narrowing involving the entire length of the thoracic esophagus.

Case 192, Fig. 2. The stomach is slightly dilated and contains a moderate amount of increased secretions. The lesser curvature of the stomach is markedly shortened and rigid (along narrows). There is a constant area of marked narrowing in the proximal portion of the antrum (arrow A). The visualized mucosa within this strictured segment appears normal.

ACKNOWLEDGMENT

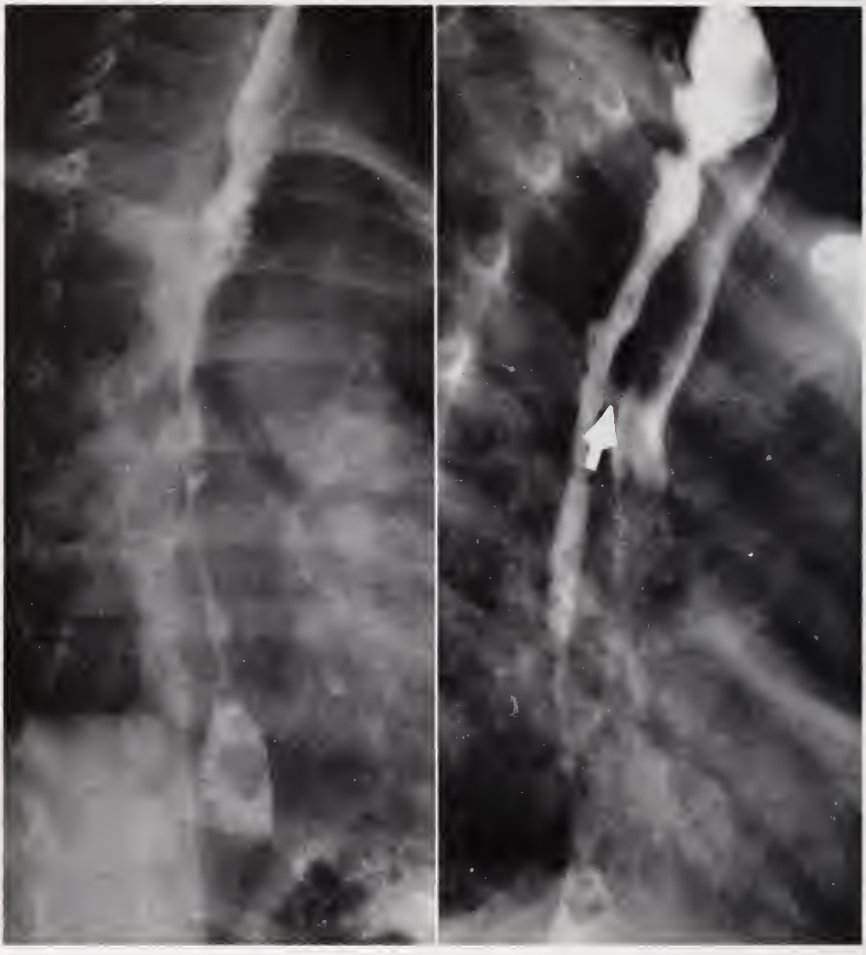
This case is presented through the courtesy of Dr. Albert S. Lyons.

See discussion after Case 193.

CASE NO. 193

A four year old girl accidentally ingested half a glassful of concentrated lye. During the first eight weeks following this episode, there was no significant dysphagia and the patient was treated conservatively with supportive measures. After a two month period, because of increasingly severe difficulty in swallowing, dilatation of the esophagus was started, with bougies passed every two weeks and left *in situ* for approximately three days. The patient did well during the two week period after each procedure at which time dilatation was again required. Radiographic examination of the esophagus revealed a 6 cm long segment of narrowing in the lower middle third of the esophagus (Fig. 1).

At the point of maximal narrowing, the lumen measured 3 mm in diameter and the mucosal folds appeared effaced, suggesting superficial ulcerations. The



Case 193, Fig. 1. Barium meal examination reveals a 6 cm long segment of narrowing in the lower middle third of the thoracic esophagus. At the point of maximal narrowing, the lumen measures 3 mm in caliber and the mucosa appears to be superficially ulcerated.

Case 193, Fig. 2. Repeat examination of the esophagus with water soluble contrast medium demonstrated a fistula joining the middle third of the esophagus to the trachea about 2 cm proximal to the carina (arrow).

esophageal segment just above the diaphragm was normal in ealiber and distensibility. The cervical esophagus was also normal. Esophagoscopy revealed a strieture 14 em distal to the upper incisor teeth. The mueosa in this region was noted to be markedly erythematous and superficially uleerated. Approximately six weeks after the first esophagoscopy and dilatation, the patient developed

bilateral lower lobe pneumonia. Repeat examination of the esophagus using water soluble contrast substance demonstrated a tracheo-esophageal fistula 2 cm proximal to the carina (Fig. 2). This fistula was felt to be secondary to the repeated esophagoscopies and dilatations in the presence of a marked chemical esophagitis. After proper medical treatment of the aspiration pneumonias, the fistula was divided and repaired and a permanent colonic substernal by-pass was performed. The patient withstood this procedure well and had a normal recovery and development.

Case Report: Lye stricture of the middle third of the esophagus.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Jerrold M. Becker.

DISCUSSION

(Cases 192 and 193)

The ingestion of lye is the most frequent cause for chemical strictures of the esophagus (1). The most common site of stricture formation in the esophagus are, in order of frequency, the lower third especially at the hiatus, the cricopharyngeus (2), the level of the aortic arch and finally at the crossing of the left main bronchus (3–5). Like all concentrated alkali, lye is able to penetrate the deeper layers of the esophagus because it causes a liquifying necrosis of the tissues. If taken in great enough quantity and concentration, the lye enters the stomach along the "magenstrasse" and is held up at the pylorus where it causes a similar severe inflammatory reaction. It is generally agreed that in twenty per cent of cases of lye ingestion pyloric stenosis develops (6–9). The relative infrequency of pyloric stenosis secondary to lye ingestion is probably related to the fact that severe spasm occurs within the esophagus and the chemical is expelled by vomiting before significant amounts reach the stomach. Also, if only a small amount of lye enters the stomach, a considerable amount can be neutralized by the acid contents of the stomach (6). On the other hand, concentrated acids have a superficial scalding effect on the squamous epithelium of the esophagus, causing a coagulative necrosis of the superficial layers of the esophageal wall thus forming a firm eschar which limits its penetration (6, 8). The delicate columnar epithelium of the stomach, however, is very sensitive to concentrated acids and a severe inflammatory reaction thus ensues. This is why the esophagus escapes stricturing in eighty per cent of acid ingestion whereas pyloric stenosis is very frequent (8, 9). It has recently been shown that the best result in prevention of strictures after lye ingestion is by the stimultaneous use of antibiotics and steroids together with supportive measures (10). The use of esophagoscopy and dilatation is important to maintain an adequate esophageal lumen for proper nutrition. The inherent dangers of this procedure in the presence of a severe chemical esophagitis are well demonstrated in the second case where a traumatic tracheo-esophageal fistula developed. Colonic by-pass, as in our case, is being used with increased frequency when a long

esophageal stricture is present. In cases of pyloric stenosis, the operation of choice is gastroenterostomy with or without associated subtotal gastrectomy.

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CASE NO. 194

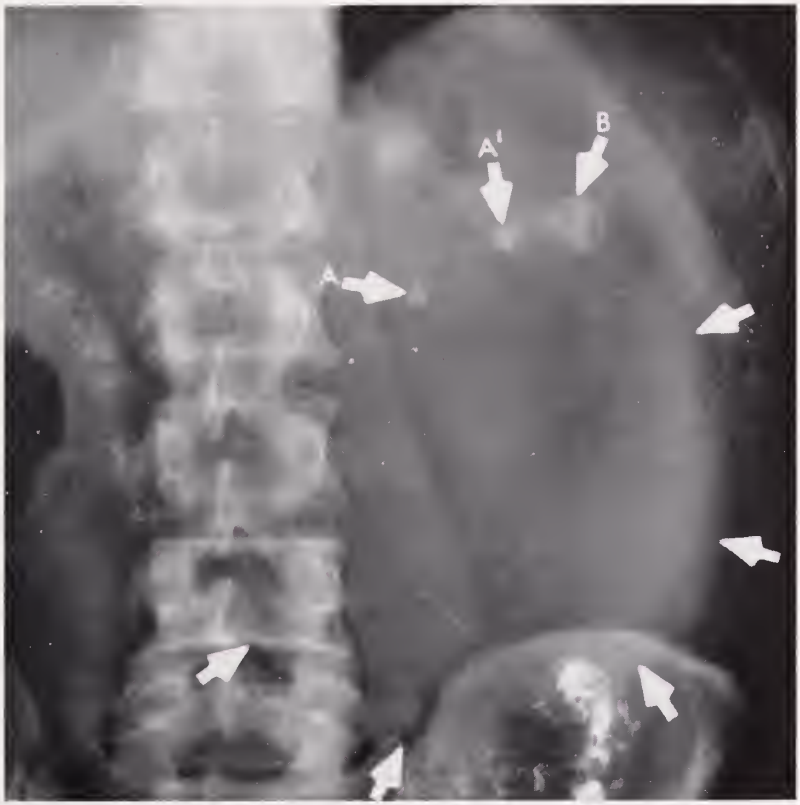
PRESENTED BY STANLEY I. WORTON, M.D.

A 60 year old male was admitted to the hospital with a two week history of productive cough and severe left upper quadrant abdominal pain. On admission a large left upper quadrant mass was palpated. Barium enema examination revealed no intrinsic abnormalities of the colon. There was a large mass in the left upper quadrant of the abdomen with a sharp lateral border displacing the splenic flexure of the colon downwards (Fig. 1). Three calcified areas were noted overlying the upper portion of this soft tissue mass. The medial two smaller concretions were homogeneous and sharply outlined and were located within the pelvocalyceal system of the left kidney. The lateral larger calcification, which measured 2 cm in diameter, was coarsely mottled and irregular in contour. The renal outlines were normal. An upper gastrointestinal series (Fig. 2) showed the mass to be displacing the stomach upward and to the right. The previously described mottled calcification was noted to lie in close proximity to the greater curvature of the fundus. The mass appeared to be fixed to the stomach at this point, causing a localized indentation. The ligament of Treitz and proximal jejunal loops were displaced downwards and to the right.

At surgery a huge cystic mass was found lying in the omental bursa behind and attached to the stomach. Believing it to be a pancreatic cyst, a 5 cm cystgastrostomy was performed through the posterior wall of the stomach. Two liters of chocolate colored material were drained from the cyst.

Postoperatively, the patient developed guaiac positive stools, falling hemoglobin, pyuria and pyrexia. A repeat upper gastrointestinal series in the fourth postoperative week, showed the barium to enter the cystic mass promptly

through a narrow cyst-gastrostomy anastomosis (Fig. 3). A markedly deformed duodenal bulb was noted with a small ulcer crater near its base. The patient's condition deteriorated and he was re-explored on the 39th postoperative day. The cyst was smaller in size, its walls were thick, and contained one liter of yellowish-red material. The cyst-gastrostomy stoma was almost close. Marsupialization of the cyst with drainage through a Pesser catheter into a stab



Case 194, Fig. 1. Postero-anterior film of the abdomen after barium enema reveals 2 small calicifications (arrows A and A') in the collecting system of the left kidney. Adjacent to these is a larger 2 cm. in diameter, coarse, irregular, mottled calcification (arrow B) near the superior margin of a large soft tissue mass (along arrows).

wound in the left lower quadrant was performed and a biopsy of the wall of the cyst was taken. Pathological examination showed extensive cystic degeneration of a gastric leiomyoma. The patient expired before a definitive operation could be performed. At autopsy a 12 cm diameter gastric leiomyoma, which had undergone cystic degeneration, was found to be attached to the greater curvature aspect of the stomach. Coarse irregular calcifications were noted to be present in the leiomyoma at its site of attachment to the stomach. Two calculi were present in the upper collecting system of the left kidney.

DISCUSSION

Calcifications in tumors of the stomach are rare. They have been reported in mucinous adenocarcinomas and leiomyomas. The calcifications in the mucous producing carcinomas of the stomach are finely stippled concretions distributed

Case 194, Fig. 2. AP view of the barium filled stomach reveals a large mass producing an extrinsic type of deformity along the greater curvature of the stomach (along arrows). The coarsely mottled calcification (arrow A) in the soft tissue mass is noted to lie in close proximity to the greater curvature of the stomach. The mass appears to be fixed to the stomach at this point (arrow B). Also noted is the previously described renal calculus (arrow C).

evenly throughout the tumor mass. In the present case, as well as in the seven previously reported ones of calcifications within gastric leiomyomas, the calcifications have been coarsely textured, irregular in outline, and more circumscribed within the soft tissue mass. They resemble the calcifications commonly seen in calcified uterine fibroids. They have been noted chiefly in the region of the attachment of the leiomyoma to the stomach.

Gastric leiomyomas are benign tumors occurring chiefly in the 5th and 6th decades of life with no sex predilection. Although most are submucosal and intra-

gastric in location, at times they present as predominantly exogastric tumors with a small endogastric component. Because they are relatively avascular, degenerative changes such as fibrosis, hemorrhage, and cystic degeneration occur. It is within these areas of necrosis and hemorrhage that the described calcifications occur. Mucosal ulcerations occur frequently at the center of the tumor and are classically known as "collar button" ulcers. The pathogenesis of the deep central

Case 194, Fig. 3. Postero-anterior film of the abdomen at the end of a barium meal reveals barium within the stomach (arrow A). Barium entered the large cystic mass (arrow B) through the cyst-gastrostomy stoma (between arrows).

ulceration is thought to be a combination of pressure necrosis of the stretched overlying mucosa and peptic digestion.

Roentgenologically, when the tumor is large and the mucosal ulceration irregular and bizarre in appearance the possibility of a leiomyosarcoma should be suggested. At times a bizarre pattern of gas has been seen within the soft tissue mass of the leiomyosarcomas which probably represents a free communication of air from the lumen of the stomach through the ulceration into the depths of the tumor.

Case Report: Calcified gastric leiomyoma.

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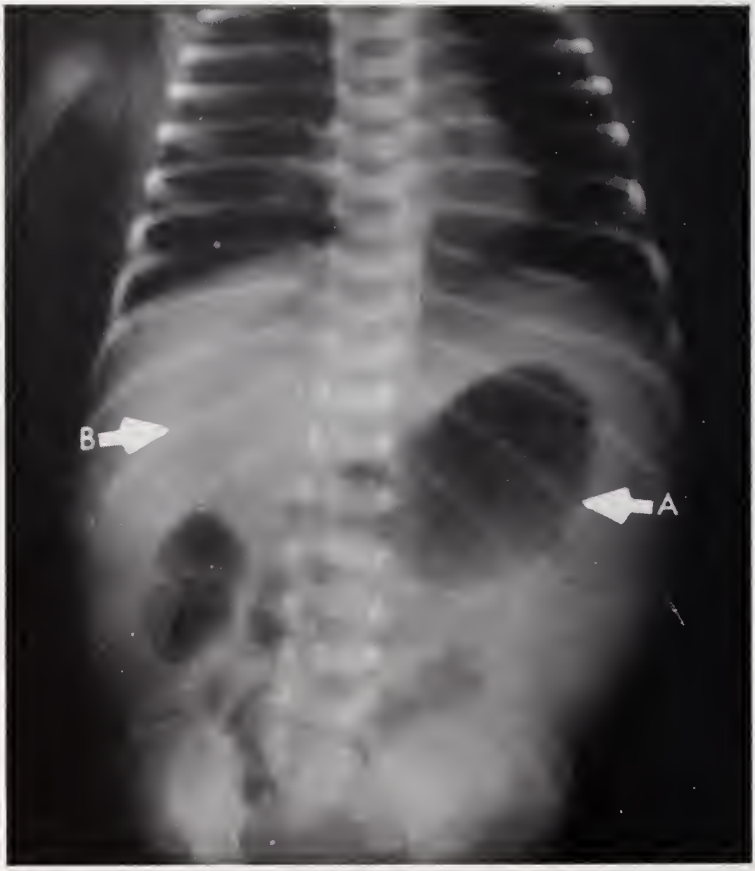
CASE NO. 195

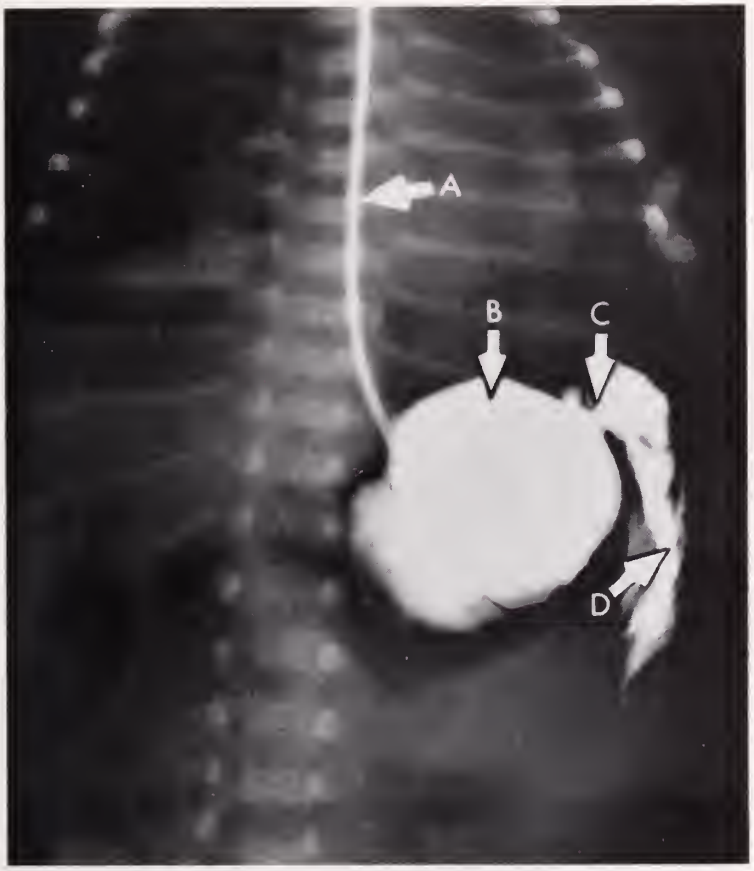
PRESENTED BY STANLEY I. WORTON, M.D.

A five day old premature male infant, weighing 2400 grams at birth was apparently well until he became listless, refused feedings, and developed abdominal



Case 195, Fig. 1. Supine film of the abdomen reveals air outlining a moderately dilated stomach (arrow A). An area of increased lucency is noted in the right upper quadrant which represents free air in the abdominal cavity (arrow B). A small amount of air is noted in the proximal portion of the small intestine.

distention without vomiting. On the morning of the sixth day, the abdomen was noted to be more distended, bowel sounds became absent, no stools were passed in the previous 24 hours, and the infant vomited small amounts of green mucoid material. A supine film of the abdomen (Fig. 1) revealed air outlining a moder-

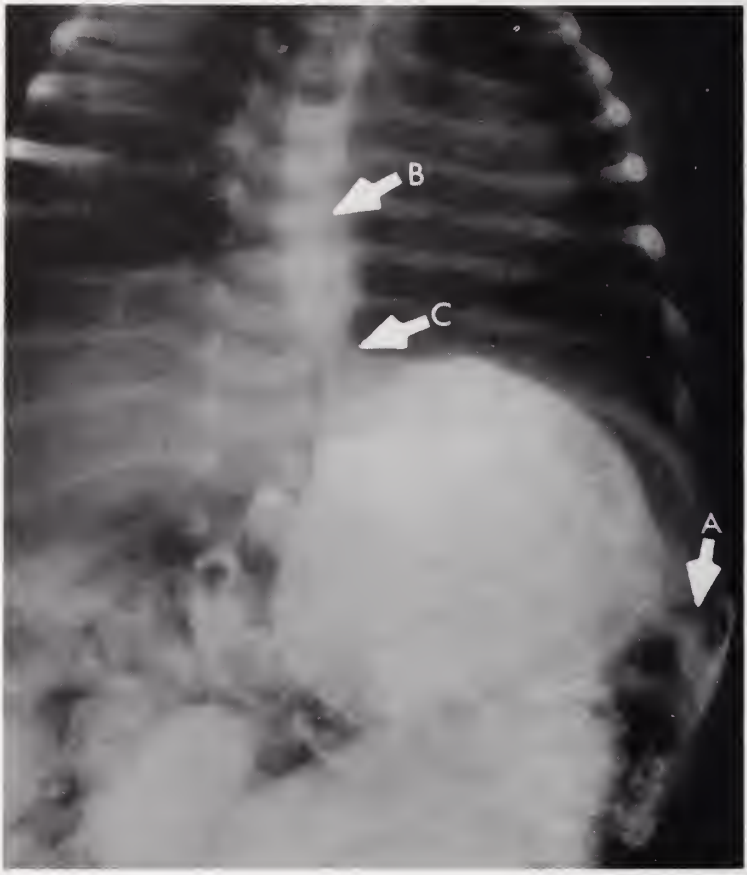


Case 195, Fig. 2. Supine film of the abdomen following the injection of 10 cc of water soluble contrast material through a nasogastric tube (arrow A), reveals the fundus of the stomach to be normally distensible (arrow B). There is a perforation of the fundus of the stomach on its greater curvature aspect (arrow C) with free passage of contrast material into the abdominal cavity (arrow D).

ately dilated stomach, and a small amount of gas in the proximal small bowel. An area of increased lucency in the right upper quadrant was interpreted as free air in the peritoneal cavity. No gas was identified in the colon. Water soluble contrast material was then administered into the stomach through a nasogastric tube (Fig. 2). The fundus of the stomach was noted to be normally distensible. A perforation high on the greater curvature of the fundus was demonstrated, with tracking of contrast material into the peritoneal cavity. An upright film

of the abdomen at this time, confirmed the presence of free air in the peritoneal cavity.

At operation, a moderate amount of bile stained exudate was found in the peritoneal cavity. Exploration of the stomach revealed a 1.5 cm perforation at the greater curvature aspect of the fundus. The perforation was in the center of



Case 195, Fig. 3. Supine film of the abdomen after the introduction of barium through a gastrostomy tube (arrow A), in the post-operative period shows free reflux of barium into the esophagus (arrow B) through the esophagogastric junction, which is normal in configuration and position (arrow C).

an oval shaped defect of the muscularis and serosa measuring 5 cm in length and 2 cm in width. The perforation was closed with continuous chromic sutures and the musculo-serosal defect was approximated with interrupted silk sutures. A Stamm-type tube gastrostomy was then performed and the tube brought out through a stab wound in the left lower quadrant.

Postoperatively, the infant developed vomiting and moderate diarrhea. A gastrointestinal series with barium administered through the gastrostomy tube,

showed chalasia at the esophago-gastric junction with free reflux of barium up the esophagus in the supine position (Fig. 3). By feeding the infant in the upright or sitting position the vomiting was easily controlled. The infant's subsequent postoperative course was uneventful.

DISCUSSION

Spontaneous perforation of the stomach in the newborn infant located high along the greater curvature is almost pathognomonic of a congenital muscular defect of the stomach (1). These infants are often premature and are usually male. Twenty-five previous cases of gastric perforation due to congenital muscular defect in newborns have been reported. Using water soluble contrast medium, the site of perforation can usually be readily demonstrated, facilitating surgical repair.

Seventy-five cases of perforation of the stomach in newborn infants have been reported (2). Only 13 have survived. This case makes the 14th known survivor. The main causes of gastric perforation in order of frequency are: Congenital muscular defect; gastric ulcer, trauma from tubes; idiopathic. Abdominal distention a few days after birth has been the most consistent clinical finding. The most important radiologic finding is the presence of free air under the diaphragms on upright abdominal films. Failure to take upright abdominal films in these cases has been a frequent cause of failure in diagnosis. Prompt surgical repair of the defect is imperative.

Case Report: CONGENITAL MUSCULAR DEFECT OF THE STOMACH WITH SPONTANEOUS PERFORATION IN A NEWBORN INFANT.

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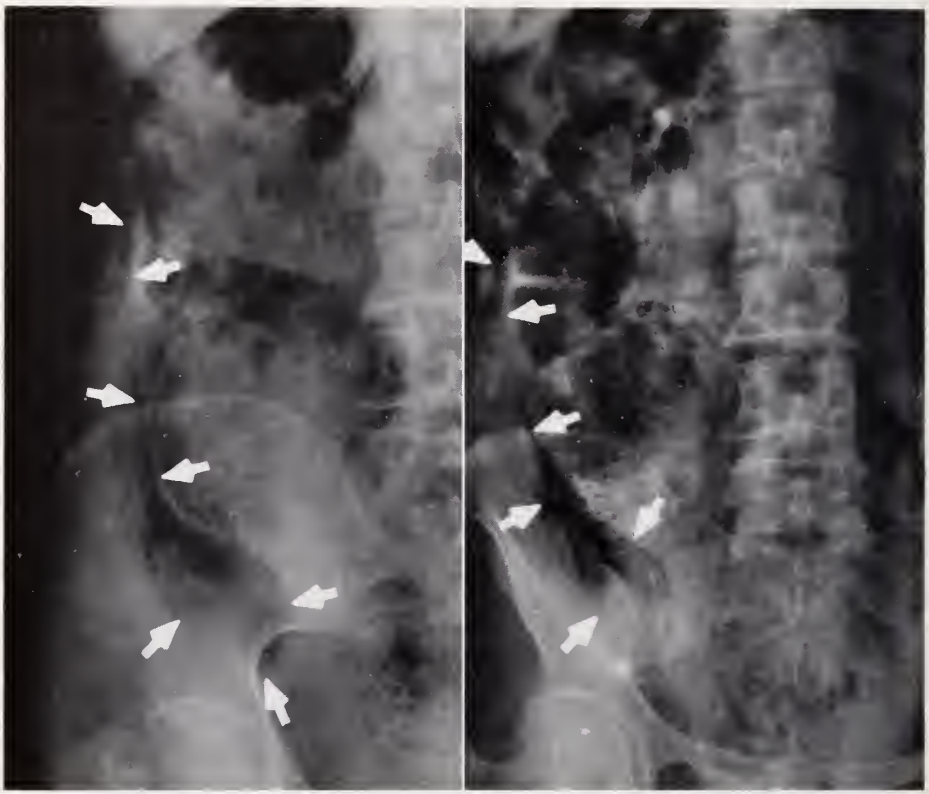
CASE NO. 196

PRESENTED BY SHELDON H. CALEM, M.D.

A 71 year old female was admitted to the hospital because of rectal bleeding and shock. There was a history of progressive constipation and intermittent vomiting during the four days prior to admission. Spotty rectal bleeding had been present for many years and was attributed to hemorrhoids. On the morning of admission the patient had an enema. This was followed by the onset of abdominal and back pain approximately two to three hours following the irrigation. The pain, originally colicky in nature, soon became diffuse and non-radiating. There was a history of steroid intake for many months presumably for rheumatoid arthritis. Physical examination on admission revealed a blood pressure of 60/0, and a pulse rate of 120 per minute. The patient was pale, cold, clammy, dehydrated and in severe distress. There was generalized abdominal tenderness, rigidity, and rebound most severe in the right lower quadrant. On rectal ex-

amination, a fungating flat lesion 2 cm from the anal orifice was palpated extending from 12 to 6 o'clock on the left lateral side of the rectum. Fresh dark blood was noted on the examining glove. The extremities were cyanotic with pitting pedal edema.



Case 196, Fig. 1. Supine projection of the abdomen. Note the curvilinear collection of air extending from the pelvis along the peritoneal wall to the region of the subhepatic area extending beyond the limits of the hepatic flexure (between arrows). Irregular mottling is noted over the right side of the abdomen obscuring the right psoas margin and extending into the pelvis.

Case 196, Fig. 2. A prone projection of the abdomen again reveals a pericolonic collection of air (between arrows) which has not changed in position with change in projection. The diffuse mottling along the right side of the abdomen and within the pelvis is again noted. There is slight distention of the right side of the colon.

Roentgen examination of the abdomen in multiple projections revealed no evidence of obstruction. There were no fluid levels within the large or small bowel, and the small bowel was normal in caliber. No free air under either diaphragm was noted. There was a crescentic, sharply delineated air collection, pericolonic in distribution, extending from the right iliac fossa to just above the

level of the hepatic flexure of the colon (Fig. 1). This collection of air did not change in position on the upright projection suggesting a retroperitoneal location. In addition, an irregular mottling was seen over the entire pelvis, extending along the right side of the abdomen, which did not conform to the bowel lumen. Scybala were not identified. The left colon was normal in caliber with moderate distention of the right colon (Fig. 2). A diagnosis of retroperitoneal perforation of the colon was advanced, occurring either in the region of the clinically palpated rectal lesion or in the area of the hepatic flexure. The latter thought was entertained because of the moderate distention of the right bowel. Also considered in the differential diagnosis were a perforated appendix with a retroperitoneal abscess and pneumatosis coli.

An emergency laparotomy revealed a perforation in the posterior wall of the rectosigmoid with exudation of air and feces into the retroperitoneal space. A transverse glassrod colostomy was performed and drainage of the pelvis and left peritoneal space was accomplished. The patient remained in shock despite blood, antibiotics, vasopressors and steroids and expired 13 hours following admission.

Postmortem examination showed the retroperitoneal space to contain approximately 500 cc of feculent material. A large swollen, distended, greenish-black discolored rectosigmoid was seen in the midabdomen. In the distal portion of the rectum, a large, flat, saucer-shaped lesion with soft rolled borders and a hard ulcerated center was seen measuring approximately 5×8 cm in diameter. The tumor mass extended through the wall of the bowel to the perirectal tissue. There was slight muscle hypertrophy and minimal lymph node involvement. The mass had encircled the lumen of the rectosigmoid nearly obliterating it. Proximal to the tumor mass, there was moderate distention of the rectosigmoid. Three centimeters proximal to the tumor mass, a gaping defect in the posterior portion of the rectosigmoid was noted measuring approximately 9 cm in its longitudinal diameter. The perirectal tissues were fecal stained.

DISCUSSION

Retroperitoneal collections have been reported due to perforation of both intra and retroperitoneal viscera (1, 2). The duodenum, ascending and descending colon and rectum usually being free of peritoneum posteriorly, may perforate directly into the retroperitoneal area and present with air surrounding the kidneys, adrenals, along the psoas muscle, or other retroperitoneal structures. Intraperitoneal structures may perforate along the root of the mesentery with air dissecting into the retroperitoneal area. The diagnosis of a retroperitoneal perforation should be entertained roentgenographically whenever a peculiar shaped constant collection of air is seen in relation to the above-named organs or along the lateral limits of the abdominal cavity. These gas collections, which are also mottled in appearance, typically do not conform to the outlines of the bowel and do not change in position with change of projection. In the case described above, the enema may have played an important role in the pathogenesis of the retroperitoneal perforation.

Case Report: Retroperitoneal perforation secondary to perforated rectal carcinoma.

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CASE NO. 197

A five year old boy was admitted to the hospital complaining of episodic abdominal pain. The illness began five days prior to admission and for three days the pains were widely intermittent, mild to moderate in degree, and poorly localized to the midabdomen. The patient was completely asymptomatic on the fourth day and had a normal bowel movement the morning of the day of admission. Later during the day, episodic pain returned with increased severity and frequency and the abdomen became distended. There was no vomiting, diarrhea or rectal bleeding.

Past history revealed numerous self-limited attacks of abdominal pain which has been ascribed to "intestinal virus" or "upset stomach." There were no previous operations.

Physical examination revealed moderate abdominal distention without local tenderness, palpable mass, or sign of peritoneal irritation. Raspberry-colored stool was observed following rectal examination. There was no fever and routine examinations of the blood and urine were within normal limits. An attack of pain was observed; the pain was localized to the midabdomen and seemed to be crampy in nature. A clinical diagnosis of intussusception was advanced by both the pediatrician and the consulting surgeon.

Plain film study revealed the abdomen filled with distended small bowel loops containing gas and fluid. Colonic outlines were not identified and there was no free air. The findings indicated a mechanical obstruction localized to the distal ileum. Barium enema examination was then performed in an attempt to delineate the exact site and nature of the obstruction. The colon was normal and the appendix was normally located. Barium traversed approximately ten inches of intact terminal ileum and then encountered the site of obstruction in relation to a 2 cm smoothly outlined ovoid filling defect (Figs. 1 and 2). A few crescent-shaped folds were delineated about the mass in a coil-spring pattern. The diagnosis of ileo-ileal intussusception was suggested with the intussusceptum led by a small polypoid lesion.

At surgery, the intussusception was found and manually reduced. As reduction was completed, a Meckel's diverticulum emerged just at the point of origin of the intussusception. The diverticulum had been invaginated into the bowel lumen and had led the intussusceptum. Although there was no indication of gangrene, an eight inch segment of reddened and edematous bowel was resected along with the diverticulum. The patient recovered uneventfully and was completely well when seen three months later.

The pathologist described a Meckel's diverticulum which contained both small bowel and gastric types of mucosae. There were extensive superficial ulcerations of the mucosa in the adjacent bowel and fecal zones of similar change in the diverticulum. Normal bowel was present at both margins of the resected specimen.

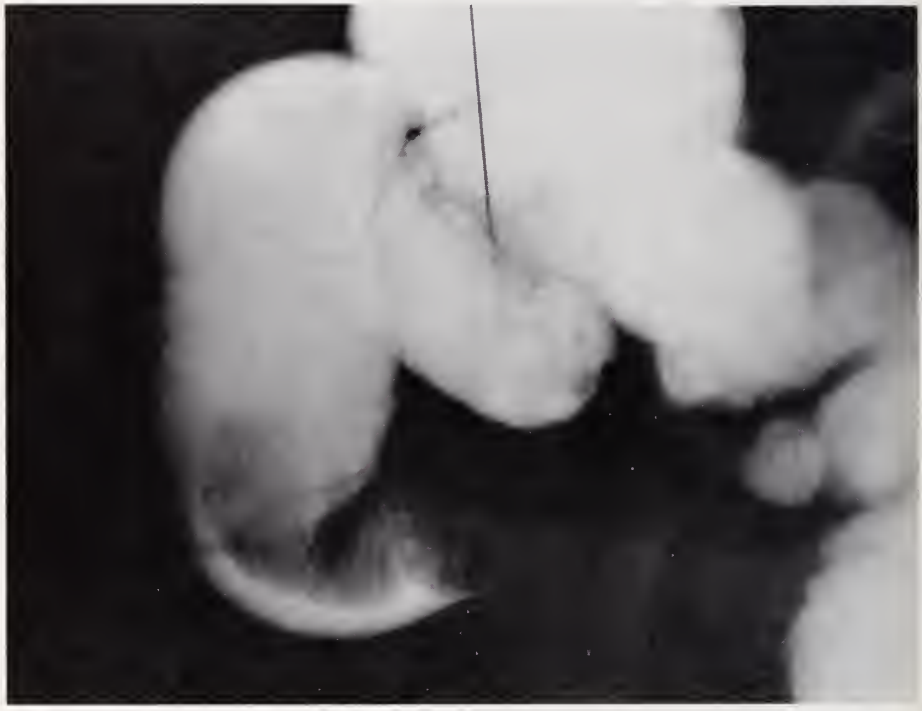
Case 197, Fig. 1. Postero-anterior view of the abdomen during barium enema examination reveals an ovoid filling defect at the site of obstruction to the retrograde flow of barium through the terminal ileum. The colon is normal and the appendix is in normal location. Gas-distended small bowel loops occupy the midabdomen.

DISCUSSION

Intussusception is the most common cause of acquired intestinal obstruction during infancy. The vast majority of cases are ileocolic or ileo-ileocolic in nature with the ileo-ileal variety being much less common. The disease is not seen in the first three months of life, and further, the association with well-nourished and obese infants is well known. These facts support the theory that prominent lymphoid tissue in the terminal ileum acts as the lead point of the intussusception in the so-called nonspecific or idiopathic cases (1). Specific etiological factors include numerous varieties of small bowel mucosal lesions and situations

with fixation of the bowel wall as well as Henoch-Schönlein's allergic purpura and mesenteric lymphadenitis.

Meckel's diverticulum is the most common specific cause of intussusception and large series have been reported (2, 3). In a series of 702 cases of intussusception of all types there were only 43 cases where a specific cause was determined; of these cases, 32 were due to Meckel's diverticulum (4). These cases are associated with the highest mortality and morbidity and bowel resection is required in about half of the cases (5). A photograph of such a resected specimen



Case 197, Fig. 2. Close-up view of the right lower quadrant again reveals the filling defect. The margins are smooth. A few crescent-shaped folds are delineated in a coil-spring pattern.

can be seen in the textbook of Benson, *et al.* (6). Whereas rectal bleeding is usually characterized by slow oozing from damaged mucosa, bright red rectal bleeding should suggest Meckel's diverticulum; ectopic gastric mucosa with acid production and peptic ulceration is generally accepted as the mechanism (7).

The usual radiographic features of ileo-ileal intussusception are those of distal small bowel obstruction with distended proximal loops containing gas and fluid. Peroral contrast study as an aid in specific diagnosis is contraindicated because of the subsequent delay to definitive therapy. Barium enema examination should be considered in every case, to be performed with careful fluoroscopy and con-

trolled hydrostatic pressure. This will eliminate confusion in certain cases between large and small bowel gas shadows. It will be diagnostic and often therapeutic in cases of classic ileocolic intussusception including those in which the intussusceptum is located just at the ileocecal valve. In this latter situation, features of small bowel obstruction coupled with a normally located nondistended colonic outline may be observed on preliminary films and the possibility of curative enema overlooked. However, even with a normal colon, an attempt should be made to reflux barium into the terminal ileum. This affords the opportunity to locate the specific point of obstruction and define the roentgen features. The information thus obtained may be of distinct advantage to the operating surgeon.

Hydrostatic reduction of ileo-ileal intussusception should not be attempted. The incidence of compromise of the bowel wall is high as is the incidence of specific mucosal lesions, and both conditions require surgical management. In considering bowel resection, the surgeon must be alert to the possibility of differential compromise of the bowel wall with mucosal necrosis and ulceration in the face of viable muscular and serosal coats. This has been illustrated and discussed in a previous communication (8).

Case Report: Ileo-ileal intussusception due to invaginated meckel's diverticulum.

ACKNOWLEDGMENT

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In Memoriam

ERNEST EMANUEL ARNHEIM

1899–1962

Ernest Emanuel Arnheim, who passed away on October 11, 1962, was born in New York City on January 4, 1899. He attended New York public schools. He received his B.A. degree from Columbia College in 1920 and his M.D. degree from the College of Physicians and Surgeons of Columbia University in 1923.

He spent his first year of internship at The Mount Sinai Hospital from 1923 to 1924. He then interned for one year at the Hospital for Ruptured and Crippled, now the Hospital for Special Surgery, and, in 1925, he returned to Sinai for another two-year internship, followed by one year as Surgical Resident in the Private Pavilion.

During this period of training, it was quite apparent to his colleagues that "Ernie" was a most trustworthy and assiduous physician. He was never too tired—always ready and willing to help his colleagues; any work delegated to him was certain of accurate completion. He had a placid disposition and performed his duties in a quiet yet diligent manner.

After entering private practice, he became associated with Dr. Albert A. Berg and remained with him for many years.

In 1929, Ernest Arnheim was appointed Adjunct Surgeon at Mount Sinai. The zeal and dependability which had been manifest during his earlier training period were always present. He developed a meticulous surgical technique, which later proved an asset in the specialty to which he applied himself. As precise as was his technique so was his scientific and devoted care given to patients.

Ernie became interested in the surgery of infants and, in 1940, in order to work with Dr. William Ladd, who pioneered the work in this field, he took a Postgraduate Residency at the Children's Hospital in Boston. Upon his return to Mount Sinai, he confined himself to the Children's Surgical Wards. He was among the first specialists in Pediatric Surgery in New York City. In 1947, he was appointed Associate Surgeon for Pediatric Surgery at Mount Sinai, which rank he held until he reached the retirement age in 1956, when he was appointed Consultant Surgeon. He was also appointed Associate Surgeon in charge of Pediatric Surgery at the Beth Israel Hospital in 1947. There, he was promoted to Attending Surgeon in 1958. He was also Consultant Surgeon to the Beth El Hospital in Brooklyn and to the following institutions in New Jersey: St. Michaels in Newark; St. Clares, Denville; Riverside Hospital, Boonton; and the Dover General Hospital. He was an Instructor in Pediatric Surgery at both Columbia University and Seton Hall.

Ernest Arnheim was a Fellow of the New York Academy of Medicine and of the American College of Surgeons; a Diplomate of the American Board of

ERNEST EMANUEL ARNHEIM, M.D.
1899–1962

Surgery; an Affiliate Fellow in Pediatric Surgery of the American Academy of Pediatrics; and a member of the New York Pediatric Society. He was a Major in the Army Reserve in 1942, but he was not called to Active Duty.

Ernie was a prolific writer; he authored approximately fifty scientific papers. In the earlier years, his articles were related to General Surgery but, later, they were concerned solely with his specialty—Pediatric Surgery. He was as precise in keeping medical records as he was in his surgical technique. The case history of every patient was written in great detail and, where indicated, illustrations were given.

His love of music was exceeded only by his devotion to his profession, and his collection of symphonic and instrumental records was voluminous.

We condole with his widow, Lian, in his sudden and untimely passing and we express to her our sympathetic thoughts. May she find solace in the knowledge that we shall always remember Ernie as a dear friend; a modest, peaceable doctor deeply respected and beloved by all who knew him—by his patients, by his friends, but, most of all, by his colleagues.

"By medicine, life may be prolong'd, yet
death
Will seize the doctor too."

Arthur H. Aufses, M.D.
for the
Editorial Board

Clinical Conference on "Allergic" Diseases of the Kidney

Edited by MARVIN H. GOLDSTEIN, M.D.
Chairman, FREDERICK H. KING, M.D.

New York, N. Y.

1. Introductory Remarks . . . . . Marvin F. Levitt, M.D.
2. Anaphylactoid Purpura (Schöenlein-Henoch Syndrome)
   Case Presentation and Discussion . . . . . Marvin H. Goldstein, M.D.
3. Polyarteritis Nodosa
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   Discussion . . . . . Donald Gribetz, M.D.
6. Concluding Remarks . . . . Marvin F. Levitt, M.D.

Chairman Frederick H. King:

The subject for this program is allergic diseases of the kidney. The idea for having this particular program arose when Dr. Levitt and I were on service together and encountered a case of anaphylactoid purpura with glomerulitis. At that time both of us realized how relatively unfamiliar we were with this entity in the adult. We were well aware that the pediatricians saw this condition rather often.

The concept that renal diseases may be due to an abnormal antigen-antibody response has the advantage of linking a number of conditions which have many clinical and histological features in common. These conditions include anaphylactoid purpura, polyarteritis nodosa, systemic lupus erythematosus, glomerulonephritis and perhaps even subacute bacterial endocarditis. With the exception of the last, we have included all of them in tonight's discussion.

Since Dr. Levitt is the organizer and head of the Section on Renal Disease, I have asked him to serve as moderator.

INTRODUCTION

Dr. Marvin F. Levitt:

Dr. King has mentioned the case that has provoked a renewed interest in the topic of allergic renal diseases and acted as a stimulus for this conference. In the past generation considerable insight has been accumulated into the pathogenetic mechanisms which underlie the development of many diverse immunologic nephropathies. Dr. Bela Schick, former chief of the Pediatric Service at The Mount Sinai Hospital was one of the first to call attention to the possibility that

Presented at The Mount Sinai Hospital, February 20, 1961.

an immune reaction might provoke the clinical picture of acute diffuse glomerulonephritis (1). He emphasized the delay period between the original illness and the subsequent development of the renal disease. Moreover, it was shown that when the nephropathy developed, bacteriological evidence of the provoking infection either in throat or urine cultures no longer existed. The experiments of Masugi demonstrated the antigenicity of rat renal tissue (2). The development of nephritic-like lesions when rabbit antirat-kidney serum was reinjected into the same species confirmed the immune nature of this reaction. The observations of Rich and others demonstrating that the repeated injections of antigenic protein into various species provoked arterial lesions similar to those observed in polyarteritis and the occasional development of the clinical syndrome after the exhibition of some antigenic stimulus or drug suggested the immune nature of this disease process (3, 4).

The development of the fluorescein stained anti-gamma globulin technique (5) has permitted the demonstration of gamma globulin within the basement membrane of kidneys with lesions of glomerulonephritis, disseminated lupus, amyloidosis and other diseases. Finally, the demonstration that the basement membrane of the glomerulus possesses a profound degree of antigenicity (6) has helped explain the frequency of glomerular damage in autoimmune diseases.

The developing field of kidney transplants have crystallized the immense need for coping with the intense antigenicity of renal tissue. In several instances of renal transplantation, the newly functioning kidney has been shown to develop a similar disease to that which prompted the original transplant (7). Specifically, a kidney replacing a shrunken glomerulonephritic organ subsequently developed glomerulonephritis or polyarteritis.

With the advent of new techniques, data and interest, it seems warranted to review in detail some of the specific diseases which presently are considered to be of allergic or immune etiology. It is our hope that after the presentations, each of you will have a more complete and informed view of the nephropathies to be discussed.

The first example of an allergic disease involving the kidney is the Henoch-Schöenlein syndrome (anaphylactoid purpura). Dr. Marvin H. Goldstein, who has been interested in this syndrome, will present a fairly typical case and then discuss some of the pertinent characteristics of this syndrome.

ANAPHYLACTOID PURPURA

Case Presentation

Dr. Marvin H. Goldstein:

The patient, a 49 year old white male, was admitted to The Mount Sinai Hospital because of a rash on his legs and joint pains of two day's duration. He had been in good health until two weeks prior to admission when he noted an erythematous bulbous eruption on his hands. He was seen in The Mount Sinai Hospital Dermatology Clinic where a diagnosis of contact dermatitis with secondary bacterial infection was made. He was treated with four injections of procaine penicillin and erythromycin for one week. During this week the patient suffered from anorexia, vomiting and diarrhea.

Two days prior to admission an urticarial, pruritic eruption appeared on the anterior surface of his legs. At that time the patient had pain in both knees and ankles. One day prior to admission the urticarial pruritic lesions disappeared but small purpuric lesions appeared over the legs and thighs. The patient's knees and ankles became swollen and more painful, and he was admitted to the hospital. There was no history of penicillin allergy, bleeding disorder, arthritis or renal disease.

On admission the patient appeared to be acutely ill, complaining of pain in his ankle and knee joints. The blood pressure was 190/90 and the temperature 100° F. Small purpuric lesions were noted on the legs, thighs, scrotum, penis and lower part of the abdominal wall. Coalescence of these lesions was noted in some areas. The remainder of the examination was negative, except for swelling of the knees and ankles with pain on movement of these joints, and modest pretibial edema.

The laboratory studies revealed a urine specific gravity of 1.015, 1 plus proteinuria, 10 to 20 white blood cells and 10 to 15 red blood cells per high power field, and occasional granular and cellular casts. The urine protein excretion exceeded 2.0 Gm in 24 hours. The hemoglobin was 14.6 Gm%, white blood cell count 9,850 per cu ml with a normal differential, and the platelet count was 420,000. The erythrocyte sedimentation rate was 36 mm in one hour. The blood urea nitrogen was reported as 28 mg%, creatinine 1.7 mg%, cholesterol 193 mg% and uric acid 6.9 mg%. The serum proteins and electrolytes were normal. An intravenous pyelography showed normal-sized kidneys with only faint visualization of the upper urinary tracts. The impression on admission was anaphylactoid purpura, probably secondary to penicillin allergy.

In the first months of hospitalization the patient's course was characterized by migratory polyarthritis, involving the knees, ankles and wrists, a decrease in the purpura, and a persistence of the hypertension and peripheral edema. At this time a skin biopsy was performed and was reported as "compatible with the diagnosis of allergic vasculitis of the anaphylactoid purpura type." Urinalyses were performed frequently with proteinuria and hematuria present on every test. During this first hospital month the blood urea nitrogen ranged between 28 and 35 mg% and the creatinine between 1.7 to 2.9 mg%. A renal biopsy was performed in the first hospital month, approximately six weeks after the onset of the illness. This biopsy was interpreted as compatible with the diagnosis of subacute glomerulonephritis.

In the second month of hospitalization the arthritis and the purpuric lesions disappeared. However, the hypertension, hematuria, proteinuria and edema persisted. Antihypertensive drugs were administered with a modest reduction of blood pressure. In the third month of hospitalization the clinical picture was that of subacute nephritis with hypertension, edema, proteinuria, hematuria and anemia as the most conspicuous features. Deterioration of renal function now became overt. The blood urea nitrogen rose to 63 mg% and creatinine to 7.7 mg%. In the last two weeks of life the clinical picture was that of severe renal failure. The patient became progressively more lethargic, stuporous and finally comatose. A pericardial friction rub was noted and gastrointestinal bleeding developed. The blood urea nitrogen rose to 88 mg% and creatinine to 12 mg% and the urine output decreased to less than 500 cc per day. The patient died after three and one-half months of hospitalization.

In summary, this 49 year old white male developed purpura, arthritis, and nephritis two weeks after penicillin was administered. Within one month all skin and joint manifestations had subsided, but the nephritis became more severe. The renal disease was characterized by hypertension, edema, proteinuria and hematuria. A kidney biopsy six weeks after the onset of symptoms was reported as showing subacute nephritis. The patient died with progressive renal failure four months after the onset of symptoms.

DISCUSSION

Dr. Marvin H. Goldstein:

Anaphylactoid purpura (Henoch-Schöenlein purpura) may be grouped with acute glomerulonephritis, rheumatic fever, systemic lupus erythematosus and

polyarteritis nodosa since each possesses certain similar pathologic, clinical and possible pathogenetic characteristics. Available evidence suggests that these disorders may result from an antigen-antibody reaction in the endothelium of certain blood vessels. In anaphylactoid purpura the small arterioles and capillaries of the skin, gut, synovia and glomeruli are affected. In one-third to one-half of the cases the proposed antigen-antibody reaction follows a beta-hemolytic streptococcal infection. However, a large number of cases have been associated with other bacterial infections; foods, including chocolate, milk, eggs, beans and strawberries; and drugs, including penicillin, sulfonamides and salicylates. It is of interest that in a recent report of five cases of anaphylactoid purpura with renal involvement, four patients received penicillin just prior to the onset of their disease (8). This particular circumstance also applies to the patient described here tonight.

There are a number of experimental studies that support the contention that the origin of anaphylactoid purpura rests on an immunologic basis. Miescher *et al.* prepared autogenous bacteria-free filtrates (of Staphylococcus or Streptococcus) from patients with anaphylactoid purpura (9). When these vaccines were administered intradermally to patients from which the organisms were obtained, purpura developed at the site of injection in every case and became generalized in two cases. In a normal control, a positive skin test could be induced only when serum from a patient with anaphylactoid purpura was injected before the administration of the autogenous vaccine. Israel *et al.* were able to produce purpura, hematuria and gastrointestinal tract bleeding in guinea pigs by the administration of anti-guinea pig-endothelium rabbit serum (10). These same workers found that the sera of patients with anaphylactoid purpura produced ecchymoses in a greater percentage of guinea pigs than did normal sera (11).

Anaphylactoid purpura associated with nephritis is a frequently observed entity in childhood, but has been only rarely reported in adults (8). Although the early reports emphasized the skin, joint and gastrointestinal tract manifestations, Henoch (12) described renal involvement as an important component more than sixty years ago. Osler recorded a fifty per cent incidence of nephritis, with death from renal failure occurring in 5 of 14 patients (13). In more recently reported studies (14–18) the percentage of cases with renal involvement ranged between 40 to 100 per cent, but the average approximated 50 per cent.

Clinically, the renal manifestations are typically indistinguishable from Type I nephritis of Ellis, and are characterized by hematuria, proteinuria, edema and hypertension. As might be anticipated, hematuria is the most common finding and has been reported in 100 per cent of the cases with renal involvement. Proteinuria is observed in more than 60 per cent of these cases, while nitrogen retention and hypertension occur in less than 25 per cent. In the majority of cases the nephritis is apparently benign, with complete clinical recovery occurring within several months. However, the high frequency of abnormal urinary findings in cases followed for ten years suggests that the absence of overt disease does not necessarily indicate complete recovery. A review of six series (176 cases) reveals that 28 per cent of the cases showed an abnormal urinary sediment,

although most had both normal clearance values and serum nitrogen concentrations. It was the persistence of abnormal urinalyses that prompted Wedgewood and Klaus to suggest that anaphylactoid purpura may be a cause for chronic nephritis in older children and adults (15). Indeed, Derham and Rogerson reported a six per cent incidence of chronic nephritis in a long term follow-up (16). In contrast to these findings, Oliver and Barnett (17) found no evidence to support the contention that nephritis was a late sequela of anaphylactoid purpura.

A small number of cases of anaphylactoid purpura have also been observed in which renal involvement was the primary manifestation of active disease. In the majority of these cases severe glomerulitis (hematuria, proteinuria and casts) is present from the onset of the disease. Renal failure is rapidly progressive and death in uremia usually occurs within several months of the onset of symptoms. The case presented here is an example of this small group.

The only laboratory test that appears helpful in differentiating the nephritis of anaphylactoid purpura from acute diffuse glomerulonephritis is the measurement of serum complement. In anaphylactoid purpura serum complement has been found to be normal, while in acute glomerulonephritis it tends to be reduced (19).

Since death from renal failure is rare, no large series of pathologic studies of anaphylactoid purpura with renal involvement have been reported. While several authors have described changes identical with Type I nephritis of Ellis, the lesion usually described is that of a widespread focal glomerulonephritis, with various amounts of focal necrotizing glomerulitis, crescent formation and focal interstitial perivascular infiltrates of polymorphonuclear and mononuclear cells. Vernier *et al.* in performing serial renal biopsies at varying intervals after the onset of disease found that the "acute glomerular lesion is characterized by segmental glomerular proliferation and occlusion of capillaries by Schiff-positive fibrinoid material" (20). These authors concluded that the pathologic lesion in anaphylactoid purpura was a diffuse vasculitis and the kidney lesion most often resembled that noted in systemic lupus erythematosus. While both proliferative and necrotizing glomerular lesions have been reported in anaphylactoid purpura, the intensity of the latter lesion correlates well with the clinical picture of rapidly progressive renal failure. Similar vascular lesions have resulted from experimentally induced antigen-antibody reactions (21).

The management of the renal abnormalities in anaphylactoid purpura is similar to that utilized in any state of salt and water retention (as in acute diffuse glomerulonephritis, congestive heart failure). This includes bed rest, salt restriction and judicious use of diuretic agents and antihypertensive agents as deemed necessary. Based on the hypothesis that anaphylactoid purpura represented the result of a hypersensitivity reaction, corticosteroids have been employed in the therapy of this disorder (22, 23). However, results of recent studies suggest that the corticosteroids do not influence the acute phase of renal involvement or the development of chronic nephritis (18).

In summary, there is experimental and clinical evidence supporting the concept that the pathogenesis of anaphylactoid purpura is based on a hypersensitivity reaction. The disease occurs most often in childhood, but adults also may be afflicted. The incidence of renal involvement approximates fifty per cent with the majority of these cases undergoing prompt clinical recovery. In the small number of cases developing rapidly progressive renal failure, necrotizing rather than proliferative glomerular lesions predominate. Corticosteroids have not proved to be effective in altering the course of the renal involvement.

Dr. Levitt:

Thank you very much, Dr. Goldstein. I think that after listening to the discussion of this first case, it is not difficult to see why polyarteritis nodosa was included on this program. The next case will be presented by Dr. Julius J. Deren.

POLYARTERITIS NODOSA

Case Presentation

Dr. Julius J. Deren:

The patient was a 43 year old white female who was admitted to The Mount Sinai Hospital for the first time in September, 1957 with fever, myalgia, polyarthritis and edema. Three months prior to admission the patient received an intramuscular injection of milk as treatment for episcleritis. A systemic reaction immediately developed characterized by fever, myalgia, polyarthritis and edema, which did not respond to steroids.

On admission her blood pressure was 140/90. Urinalysis revealed 2 plus proteinuria with many red blood cells per high power field. L.E. preparations were negative. A skin and muscle biopsy showed "fragments of striated muscle with two small arterioles showing acute necrotizing arteritis, suggestive of periarteritis nodosa."

The patient was discharged on steroid therapy but was readmitted to Mount Sinai Hospital two weeks later in acute pulmonary edema. On admission the blood pressure was 170/116 and the pulse rate 120/min. She responded well to standard therapy for acute pulmonary edema. The laboratory findings on this admission included a urinary specific gravity ranging from 1.008 to 1.010, 2 to 3 plus proteinuria, and persistent microscopic hematuria; white blood cell count ranged between 10,000 and 40,000 per cu ml; BUN was 25 mg% on admission but rose subsequently to 42 mg%.

One week after admission the patient began to complain of muscle weakness and numbness. Deep tendon reflexes at the knees and ankles disappeared and sensory changes were noted. During her subsequent hospital course the patient had a number of episodes of respiratory difficulty. Despite high steroid dosage, the patient died following a prolonged hypotensive episode.

Autopsy revealed acute and chronic lesions involving the vasculature of the heart, lungs, liver, pancreas, kidney, adrenal, stomach and small intestine compatible with the diagnosis of polyarteritis nodosa.

In summary, this patient was a 43 year old woman who had evidence of a systemic reaction following a milk injection, which progressed into a picture of congestive heart failure and death in shock.

Dr. Levitt:

This case will be discussed by Dr. Gilbert M. Eisner.

DISCUSSION

Dr. Gilbert M. Eisner:

It is tempting to relate the onset of the disease in tonight's case to the parenteral administration of milk. In 1942 Rich reported polyarteritis nodosa developing in patients treated with horse serum, sulfonamides, or both (3). The symptoms usually began several days after the administration of these agents and in most cases terminated fatally in a matter of weeks. Since that time there have been numerous other case reports describing the development of polyarteritis nodosa after the administration of a host of substances. The list includes thiourea, dilantin, arsenicals, bismuth, iodine, penicillin, streptomycin, chloramphenicol, gold and cortisone. Now we can add another to the list—milk.

In a series of experiments Rich and Gregory administered large single doses of horse serum to rabbits and found arterial lesions throughout the body which were identical to those of polyarteritis nodosa (4). In many of these rabbits glomerulonephritis was noted as an incidental occurrence. The vascular lesions involved not only the medium-sized and small arteries, but often arterioles and capillaries as well.

There has been a great deal of evidence suggesting a possible allergic nature of the disease. Workers, in reviewing postmortem material, have reported an increased number of plasma cells in the reticuloendothelial system and also in the periarteritic infiltrate (24). Other investigators utilizing the fluorescein staining technique have demonstrated gamma globulin to be present in the arterial lesions (25). However, the case for an allergic etiology is not conclusive. Rats made hypertensive by wrapping a kidney in silk or cellophane develop polyarteritis-like lesions (26). These lesions can also be produced in unilaterally nephrectomized rats when hypertension is produced by prolonged DOCA administration (27).

Dr. Zeek and her co-workers have presented considerable evidence to support the hypothesis that polyarteritis nodosa must be distinguished from what they have termed hypersensitivity angiitis (28). In this group, the diagnosis of polyarteritis nodosa is based upon the demonstration of lesions located at branchings and bifurcations of medium-sized muscular-type arteries. The lesions involve all layers of the arterial wall and consist of a definite inflammatory reaction as well as fibrinoid necrosis. In a single case it is usually possible to see lesions of all stages ranging from acute to healed. Renal infarcts are common, but there is minimal involvement of the glomeruli. In contrast to these findings, the lesions seen in hypersensitivity angiitis affect mostly the arterioles, venules, capillaries and small arteries, are usually all of the same age and the kidney and heart are particularly involved. Often there is an associated acute necrotizing glomerulitis. Although complete recovery sometimes occurs, the course in the fatal cases is generally more rapid than in polyarteritis nodosa, and most patients succumb in less than one month. Another distinguishing feature is the fact that in polyarteritis nodosa the gastrointestinal tract is heavily involved, whereas there is

a greater tendency to involvement of the pulmonary system in hypersensitivity angiitis.

The pulmonary involvement has been used as a distinguishing characteristic by Rose and Spencer in the series reported from England (29). Although this feature did not, in their opinion, constitute a separate disease, these workers did point out that the patients with lung involvement show features not seen in those who have classical polyarteritis nodosa without involvement of the lungs. Respiratory symptoms were present in 100 per cent of those with pulmonary lesions and eosinophilia was much more common than in the other group. Polyarteritic lesions in the kidney were found with equal frequency in both groups, but the incidence of glomerulitis in those with lung involvement was double that in the cases without lung involvement. Despite these findings, hypertension and deaths from renal failure were more frequent in the group without lung involvement. A great many of the patients in this series had received sulfonamides because of respiratory infections, but Rose and Spencer were unwilling to accept these agents as the etiologic factor for the vascular disease. Instead, they concluded that bacterial antigens might be responsible, although they could not thoroughly document this viewpoint.

Although the distinctions between various types of angiitis may have some validity, additional information does not support their separation. There have been case reports of polyarteritis nodosa associated with acute or subacute glomerulonephritis (30). Although some authors have held that hypertension alone, whether primary or secondary to renal disease, may produce lesions similar to polyarteritis, the description and distribution of the lesions in many of these case reports of nephritis are sufficient to exclude hypertension as the etiological factor.

In studies in the rat, Hawn and Janeway injected different fractions of bovine serum and found that purified gamma globulin produced a high percentage of acute nephritis, whereas purified albumin produced mainly vascular changes (21). In the kidneys these vascular lesions involved the arcuate arteries. Furthermore, in the series of human kidney transplants reported by Hume *et al.* (7), a transplant received by a patient with polyarteritis nodosa developed changes typical of glomerulonephritis.

At this time it seems reasonable to conclude that hypersensitivity angiitis and polyarteritis nodosa, if not identical, are at least closely related and very likely have a generic etiology in some type of hyperimmune reaction. The exact form of the response may be related to the nature of the antigenic stimulus, and it is very possible that autoimmune antibodies are involved.

For clinical purposes, 60 to 90 per cent of the patients with polyarteritis nodosa have shown evidence of renal involvement, either proteinuria or hematuria, or both. Since proteinuria is not usually massive, polyarteritis nodosa rarely, if ever, is associated with the nephrotic syndrome. Hypertension appears in approximately sixty per cent and terminal renal failure is reported in approximately fifty per cent of cases. Hypertension and proteinuria or hematuria are very often the initial findings in polyarteritis nodosa. The hypertension, and to

a lesser extent renal failure, seem best correlated with the presence of healed or healing arteritic lesions. Apparently the ischemic factor is far more important than the inflammatory process. This has extremely important implications, since it touches on the question of therapy.

Steroids have been used in the treatment of polyarteritis nodosa for over ten years now, and there is still no agreement on their real value. In many cases they suppress symptoms, but many workers have expressed concern that while they are successful in promoting healing of the lesions they may actually be shortening the patient's life, since the resultant ischemia will prove more harmful than the inflammation. Several of the early reports of the use of ACTH or cortisone seemed to support this possibility (31, 32). Unfortunately, a good long-term study of the effects of steroids is not available. The best is probably that reported by the British Medical Research Council, in which twenty-one patients were followed for a period of at least three years and compared with a group of untreated cases (33). It was found that when hypertensives were excluded, approximately sixty per cent of both treated and untreated patients survived three years or more. Despite the fact that some complete remissions were obtained following the use of cortisone, it was impossible to conclude that cortisone improved the changes of ultimate recovery, although it was thought that it may have prolonged life.

In summary, considerable evidence suggests that polyarteritis nodosa is caused by a hyperimmune or allergic mechanism. There appears to be some variety in the precise form in which it may be present, just as in the larger overall category of allergic diseases there is a spectrum of pathological states. Renal involvement is common in polyarteritis nodosa with the earliest manifestations being proteinuria, hematuria and hypertension. The renal damage is due mainly to the ischemia produced by the arteritic lesions. The value of steroid therapy remains uncertain.

Dr. Levitt:

The next disease entity to be discussed is systemic lupus erythematosus (SLE) and the case will be presented by Dr. Norman K. Bohrer.

SYSTEMIC LUPUS ERYTHEMATOSUS

Case Presentation

Dr. Norman K. Bohrer:

A 14 year old white female was first admitted to Mount Sinai Hospital in July, 1959 for a renal biopsy. Eighteen months prior to admission the patient had a blotchy erythematous rash over the bridge of the nose and cheeks which was aggravated by sunlight. Shortly thereafter migratory polyarthritis developed, involving the knees, ankles and wrists, with fever ranging up to 105° F. An L.E. preparation was positive. Treatment with prednisone produced a prompt remission of symptoms. Thereafter, she was maintained on prednisone as well as penicillin and oral diuretics. However, the patient continued to complain of intermittent mild arthralgias and low-grade fever.

She was first seen in The Mount Sinai Hospital Outpatient Department in May, 1959. At that time her blood pressure was 130/110. She was moderately obese with some facial puffiness and 1 plus peripheral edema. An L.E. preparation was positive. Urinalysis showed 3 plus protein and granular and hyaline casts.

In July, 1959 she was admitted for renal biopsy. At that time her blood pressure was 115/75. The patient had Cushingoid features and moderate abdominal distention. The remainder of the physical examination was unremarkable. Laboratory studies showed a hemoglobin of 11.6 Gm% and a white blood cell count of 5,850 per cu ml with a normal differential. Additional results included a platelet count of 145,000, erythrocyte sedimentation rate of 85 mm in 1 hour, serum albumin of 3.7 Gm%, and serum globulin of 2.8 Gm%. The blood urea nitrogen and liver function studies were normal and the blood serology was negative. Urinalysis revealed a specific gravity varying between 1.012 and 1.030, proteinuria ranging from 1 to 4 plus, and many red blood cells and white blood cells per high power field. The urinary protein concentration was 2.9 Gm/L. A right renal biopsy was performed in the second hospital week and the patient was discharged two days later.

In October 1959, the blood pressure was recorded as 150/110 and by April 1960 her blood pressure had risen to 180/110. At this time, she had herpes zoster-like skin lesions. Several weeks later a cough productive of yellowish sputum, and progressive anorexia became prominent symptoms.

Her final admission was in May 1960. At that time her blood pressure was 175/110. Examination of the fundi revealed grade 1 hypertensive changes. Except for Cushingoid facies and residual herpetic vesicles, the remainder of the examination was unremarkable. The laboratory studies were similar to those on the previous admission except that hemoglobin was 8.7 Gm% and blood urea nitrogen 29 mg%. Eight days after admission the patient developed focal left sided seizures. When calcium gluconate failed to control these seizures she was treated with dilantin and phenobarbital. During this period the hemoglobin fell and the blood urea nitrogen rose. When the dose of steroids was increased, tachypnea, a marked increase in edema, and a diastolic gallop were noted. The patient expired during the third hospital week during an episode of ventricular tachycardia. Postmortem examination showed the typical pathologic changes of systemic lupus erythematosus with severe renal involvement and polyserositis.

In summary, this 14 year old girl with a classical picture of systemic lupus erythematosus showed progressive renal involvement within eighteen months after the clinical onset of her disease despite steroid therapy. She died 26 months after onset of her illness with hypertension, uremia and cardiac failure.

Dr. Levitt:

This disease entity will be discussed by Dr. Lawrence Berger.

DISCUSSION

Dr. Lawrence Berger:

Early studies of systemic lupus erythematosus were concerned chiefly with pathologic and clinical findings. The work of Hebra in 1845 (34) led to a description of lupus erythematosus as a disease of the skin. Kaposi (35) and Osler (36) subsequently recognized the existence of systemic manifestations. The basic studies of Baehr (37), Klemperer and co-workers (38), Libman and Sacks (39), and Gross (40), as well as work of Reifenstein (41) and Keith (42), led to a better clinical understanding of systemic lupus erythematosus (SLE) and to an elucidation of the pathology. Hematoxylin bodies were first recognized by Gross (40) and were suggested to be pathognomonic of systemic lupus

erythematosus by Klemperer and co-workers (38). These workers also first identified the wire-loop lesions of the glomerulus. The term "collagen disease" was introduced by Klemperer to describe SLE and related diseases which primarily affected the connective tissue of the body (43). The concept of "collagen diseases" led to a better understanding of SLE and associated diseases, and helped explain their protean visceral manifestations.

The clinical syndrome of systemic lupus erythematosus was described originally as one of fever, rash and multisystem involvement. While postmortem examination showed renal involvement in 70 to 90 per cent of cases, no significant role in the clinical picture was assigned to it until the work of Baehr (37) and others (44, 45).

With the development of the L.E. preparation as a useful diagnostic test in 1948 (46), and subsequently with the therapeutic response to steroid administration, two important events occurred: 1) more diagnoses of SLE were established in life, and 2) patients with this disease survived for longer periods of time. Consequently, clinical manifestations of renal involvement became more conspicuous.

Although Keil in 1937 (47) had mentioned the appearance of what he called nephrosis in some patients with SLE, the nephrotic syndrome became more commonly recognized after 1948. Thus, in a recently reported series (48), in ten of 33 patients either a nephrotic syndrome or a pseudonephrotic syndrome developed at some point in the course of their disease. This latter entity is characterized by all the usual findings of the nephrotic syndrome save hypercholesteremia, and is important because of its alleged poor prognosis. In a recent review of forty cases of nephrotic syndrome, Kark and his colleagues (49) found seven cases to be due to SLE.

Since clinical renal involvement is being reported currently in 58 to 65 per cent of patients with SLE, it might be informative to consider briefly the character of this nephropathy. Not all cases with renal involvement manifest a nephrotic syndrome. A few may present with a syndrome simulating acute nephritis, with hematuria, edema and hypertension. Many may show evidence of the so-called "subacute nephritis" phase, either in the form of a nephrotic syndrome, or by the presence of proteinuria, formed elements in the urinary sediment, isosthenuria, and modest azotemia. Hypertension is present in only about 13 per cent of cases, and is not an invariable concomitant of lupus nephritis. In current reports, almost invariably the cause of death is renal failure, a finding substantiated by Muehrcke *et al.* (48), McCombs and Patterson (50), and Soffer (51).

Finally, I would like to dwell on the factors that suggest an immunologic basis for systemic lupus erythematosus. Three separate lines of evidence may be considered: 1) the dominant renal involvement in relation to previously known information concerning the antigenicity of kidney tissue; 2) the comparability of the connective tissue lesions of SLE to experimentally induced hypersensitivity states, and 3) the existence in SLE of multiple immunological phenomena, all indicative of auto-antibody production.

The antigenicity of kidney tissue and its capacity to induce formation of nephrotoxic antisera when injected into another species was shown first by Lindemann in 1900 (52). Antiserum, injected into the donor species, was capable of inducing pathological changes closely resembling human nephritis. In the 1930's Masugi (53) and Smadel (54) extended these observations, and later the localization of the nephrotoxic antisera in renal glomeruli was demonstrated by use of antisera labeled either with fluorescein (55) or radioactive iodine (56).

The antigenicity of basement membrane, the primary localization of anti-kidney antibodies to basement membrane, and the capacity to inactivate antiserum by exposing it to kidney antigen of the donor species, were also demonstrated (57). This line of evidence suggested the possibility of a comparable immunologic basis for human renal disease.

The studies of Rich and co-workers (58) further strengthen this possibility by demonstrating a similarity of the lesions of experimentally induced hypersensitivity states to those of the collagen diseases, including SLE.

The strongest evidence suggesting an immunologic basis for the lupus nephropathy derives from the findings of many different auto-antibodies in SLE (59). Thus: 1) an auto-antibody exists which may react with the patient's own red blood cells and cause a hemolytic anemia; 2) one or more gamma globulins exist which may react with nucleoprotein, a reaction which appears to be the first step in the L.E. cell phenomenon, and perhaps in the development of hematoxylin bodies; 3) platelet agglutinins may be found; 4) an antithromboplastic antibody may exist, which may produce a hemorrhagic diathesis; 5) a gamma globulin capable of reacting with a fraction of beef heart is the basis for the frequently found false positive test for syphilis; 6) antibodies against certain cytoplasmic constituents, such as mitochondria, may be found; 7) antibodies to blood group substances are more apt to develop in patients with SLE; 8) low serum complement levels have been demonstrated in SLE; these levels rise with remission, thus suggesting an antigen-antibody reaction with complement fixation during the active phase of disease; 9) as mentioned earlier, studies with labeled antibodies reveal localization of a gamma globulin in renal lesions. These antibodies may be recovered by eluting at an acid pH, and can then be reacted with glomeruli and shown to localize on nuclei of kidney cells. Furthermore, the gamma globulin of patients with SLE has been shown to bind to nuclear material of autologous, heterologous and homologous tissues.

The histopathological findings on renal biopsy in the glomeruli in systemic lupus erythematosus patients most commonly include basement membrane thickening, wire loops, fibrinoid changes, and endothelial proliferation (48). The only finding considered pathognomonic, the hematoxylin body, is rarely found in the glomerular sample of a renal biopsy. Areas of glomerular hyalinization and necrosis may also be seen. Increased quantities of PAS-positive material within the glomerulus, located mostly in the basement membrane, may be demonstrated. Fluorescein labeled anti-human serum globulin antibodies are seen to follow predominantly the distribution of basement membrane (60). Electron microscopic examination of the glomerulus shows thickened basement mem-

brane with abnormal deposits localized along the endothelial border of basement membrane. This lesion is considered characteristic of SLE (61).

The primacy of basement membrane involvement in SLE, the localization of antibody in the basement membrane, the fact that basement membrane is the most potent antigen for induction of nephrotoxic antikidney antisera, and that basement membrane is the most prominent localization for nephrotoxic antisera, all strongly suggest that an altered immunologic state exists in SLE. This altered immune mechanism appears capable of inducing autoantibody formation, with subsequent damaging union of antigen and antibody occurring in various tissue cells. Whether this phenomenon is primary and the cause of the disease or a secondary effect related to injury either to tissue or the immune mechanism remains to be ascertained. In this latter regard, it should be mentioned that thus far the LE cell phenomenon has only under unusual circumstances been demonstrated *in vivo*. Furthermore, cells in tissue culture grown in the presence of lupus sera containing antinuclear and anticytoplasmic antibodies have not shown any impairment of growth. Finally, it has not been possible to produce experimentally an antinucleoprotein antibody in animals.

The problems in SLE remain as fascinating today as in earlier days. This disease state offers a mirror in which may be reflected answers to questions of tissue antigenicity relevant to other disorders.

Dr. Levitt:

Thank you, Dr. Berger. The final entity to be discussed tonight will be glomerulonephritis. This disease, although not uncommon in the adult, occurs more frequently in childhood, and the case to be presented by Dr. Melvin Hollander was seen on the Pediatric Service.

GLOMERULONEPHRITIS

Case Presentation

Dr. Melvin Hollander:

The patient, a 10 year old male, was admitted to The Mount Sinai Hospital for the first time in December, 1960 with the chief complaint of swelling about the eyes. Three weeks prior to admission, he had a sore throat, cough and fever of 103° F. Six days prior to admission, the patient's face was noted to be edematous. The urine color was normal. He was brought to The Mount Sinai Hospital Emergency Room where his blood pressure was found to be 124/76. There was minimal facial edema. Urinalysis revealed 4 to 6 red blood cells and 6 to 8 white blood cells per high power field. The erythrocyte sedimentation rate was 40 mm per hour. During the next few days no facial puffiness was noticed. The child returned for admission however because of the return of facial edema and the occurrence of smoky red urine.

The physical examination on admission revealed a temperature of 99° F, blood pressure 130/90, pulse 120, and respiration 20. The patient was a well-developed, well-nourished, pasty-looking male in no distress, with questionable periorbital edema. There were no rashes and the skin turgor was good. Examination of the chest, heart and abdomen were within normal limits. There was 1 plus pretibial edema. There were no neurologic abnormalities.

The admission laboratory analysis revealed a hemoglobin of 10.0 Gm%, a white blood

cell count of 8200 per cu ml with a normal differential, and an erythrocyte sedimentation rate of 38 mm in one hour. Urinalysis revealed a specific gravity of 1.013, 1 plus proteinuria, many red blood cells and 15 white blood cells per high power field. The blood urea nitrogen, creatinine and electrolytes were all normal. The electrocardiogram was normal. The roentgenogram of the chest revealed an enlarged cardiac silhouette and pulmonary congestion. Beta-hemolytic Streptococcus was obtained from a culture of the nasopharyngeal contents. The anti-Streptolysin-O titer was reported as 833 units.

On the night of admission the blood pressure rose to 140/90, and the patient was given intramuscular reserpine. The remainder of the therapy consisted of bed rest, modest salt restriction and penicillin. By the fifth hospital day the patient had lost approximately two and one-half pounds. For several weeks urinalyses continued to show a trace of protein and 10 to 15 red blood cells per high power field. A chest film four days after admission revealed a reduction in size of the cardiac silhouette and normal lung fields. The patient was discharged four weeks after admission.

Dr. Levitt:

I will call on Dr. Donald Gribetz who will discuss the subject of glomerulonephritis.

DISCUSSION

Dr. Donald Gribetz:

This child demonstrated two or three of the clinical characteristics which originally suggested that acute glomerulonephritis was etiologically based on an immune mechanism. The child had a streptococcal infection three weeks prior to his admission. This was followed by a latent period during which a renal disease was developing which manifested itself by gross hematuria. It was the two facts—the latent period following a streptococcal infection, and the inability to isolate streptococci from the blood or the urine of the child during the actual disease—that made people suspect that some immune mechanism related to streptococcal infection was involved in the production of this renal disease.

It might be profitable to review two lines of evidence which have elucidated the pathogenesis of acute diffuse glomerulonephritis. One is the production of nephritis in the experimental animal. The second is the attempt to find antibodies to kidney tissue in the human. Perhaps it would be of some value to briefly review exactly how the first type of experimentation is performed (62). Kidneys of large rats weighing between 300 to 350 grams are suffused with saline in an attempt to make them bloodless, and then removed and stripped of their capsules and pelves, so that chiefly cortical tissue remains. These kidney cortices are homogenized, made into a saline suspension and tested for sterility. The kidney suspension is then injected into an animal of another species. In our work we used the rabbit according to the technique described by Heymann and Lund (63). This kidney suspension is injected into rabbits in graded doses over a period of three weeks. During this time presumably the rabbit is developing anti-rat kidney antibodies in its serum. The rabbit is then bled, and the serum injected into small rats of the same original strain. Within two to three days signs of renal disease usually develop in the recipient rats.

The type of kidney disease produced is rather non-specific, in that either the picture of acute nephritis or the nephrotic syndrome may be produced. Notwithstanding, this type of preparation serves as a good experimental model to study either nephritis or nephrosis, or both. In addition to presenting a model in which both the physiological and pathological changes may be studied, this experimentally induced kidney pathology offered a means to pinpoint the immunological mechanism.

Using this type of methodology, an antibody has been found in the gamma globulin fraction of the serum proteins. By the use of radioisotope or fluorescein staining techniques, it has been demonstrated that this antibody is located in the basement membrane of the glomerulus.

The second type of experimentation concerns itself with an attempt to demonstrate antibodies to kidney tissue in the human. This work has been stimulated chiefly by Witebsky's studies (64) in auto-immunization in thyroid disease. There have been several attempts to duplicate this work in terms of kidney disease. Lange *et al.* (65) was one of the first to use collodion particles which were coated with kidney tissue in an attempt to stimulate antibody production. Liu and McCrory (66) and then Goodman (67) used the hemagglutination technique. Although the approaches seem to offer promise, thus far the results have been rather inconsistent and difficult to interpret.

The treatment of glomerulonephritis in childhood is a less difficult problem than that of the other diseases discussed tonight because, as compared to these other entities, glomerulonephritis has a lower morbidity and an extremely low mortality. Since 90 to 95 per cent of children with acute glomerulonephritis recover, therapeutic efforts are directed to the management of the initial symptoms and the prevention of complications. The children are put to bed. Protein intake is not limited. Salt intake is restricted if hypertension or edema is present. Penicillin is administered for ten days in order to eradicate any streptococci.

The three complications seen in the acute stage of glomerulonephritis which may require attention are hypertension, cardiac failure and acute renal failure.

Hypertension is treated in the simplest manner possible, often only with phenobarbital. For years the classical drug has been magnesium sulfate which is given intramuscularly or intravenously. In recent years a combination of hydralazine and reserpine has been shown to be very effective in controlling the hypertension (68). For cardiac failure digitalis is employed. Acute renal failure, fortunately, is usually transitory in acute nephritis. However, on one occasion a child on the Pediatric Service had to undergo hemodialysis after four days of anuria.

One word about steroids—it is the consensus that these agents offer no advantage in the treatment of the ordinary case of acute nephritis. In a disease in which 95 per cent of the children recover, it is extremely difficult to evaluate a new therapeutic agent. When steroids were first used some ten or twelve years ago for nephritis, it was found that they did not alter the recovery rate, and, therefore, they have not been used in the treatment of acute nephritis.

This is in contrast to the use of these agents in the nephrotic syndrome of childhood where the outlook has been greatly improved (69).

CONCLUSION

Dr. Levitt:

The potent antigenic nature of renal tissue has been emphasized in the preceding discussions. It has been reported that this antigenic quality resides primarily within the glomerulus (specifically in the basement membrane) and to a lesser extent within the renal vessels. The biochemical features that account for the characteristic antigenicity of these tissues *per se* or after combination with foreign proteins remain unknown. It is apparent, however, that this unique trait explains the frequency with which these structures are involved in diverse disease processes. The specific manifestations of the separate diseases depend upon the precise structure(s) involved in the immunologic reaction. An ultimate understanding of the course of each disease state will demand a clearer explanation of the factors that sustain the antigenic stimulus in some instances or suppress the challenge in others. An analysis of the alterations that are induced by the combination of antigen and antibody may provide more basic therapeutic techniques. Finally, as the factors underlying the antigenicity of renal tissue are unravelled, the potential of organ transplant may be realized.

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Pathology of Lupus Nephritis

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Nephritis has become the leading cause of death in systemic lupus erythematosus. This development is fairly recent, dating from the introduction of steroid therapy. Formerly the characteristic glomerular changes in this disease had not been considered an important factor in the early death of patients. Steroid therapy has beneficially affected the clinical course of lupus and has modified the appearance of the renal lesions (1). The pioneering studies of Klemperer and co-workers provided a clear description of the renal changes found at autopsy of cases of systemic lupus (2). The introduction of renal biopsy made it possible to evaluate more precisely the progress of the renal disease and the effects of steroid therapy on the glomerular changes (1, 3). The standard light microscopy which had been used for the earlier studies of postmortem material was soon supplemented by phase microscopy (4) and by electron microscopy (5–7).

METHODS AND MATERIALS

A total of 38 patients were examined, 20 of these by biopsy and 25 at autopsy. In all cases the typical clinical picture of systemic lupus was present and the L.E. test, used routinely, was positive. As in our earlier studies (8), the autopsy specimens were stained with hematoxylin-eosin, periodic acid-Schiff (PAS) reagent, chromotrope-anilin blue, and periodic acid-silver methenamine, and examined by light microscopy. Biopsy specimens were divided into two parts: one part was fixed in neutral formalin, embedded in paraffin, sectioned, and stained like the autopsy material; the other was fixed in osmic tetraoxide (OsO_4) and embedded in methacrylate or epon. Sections about 0.5 μ thick were stained with periodic acid-Schiff reagent for light microscopy. For electron microscopy suitable sections were cut from the same blocks and examined in the Phillips 100 B electron microscope either unstained or after staining with uranyl, lead, or phosphotungstic acid.

RESULTS

Biopsy material

All elements of the glomerulus were found to be involved, especially the capillary walls and the intercapillary spaces. Electron microscopy revealed striking changes of the basement membrane of the capillary walls, consisting of thickening, mottling and fibrillarity. Thickening, up to four times normal, was present in

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every case. This was often accompanied by electron-dense granular material within the thickened area, a change which may be regarded as the earliest stage of "wire loop" (Fig. 3). When thickening was irregular, the outline of the basement membrane appeared scalloped (Fig. 5).

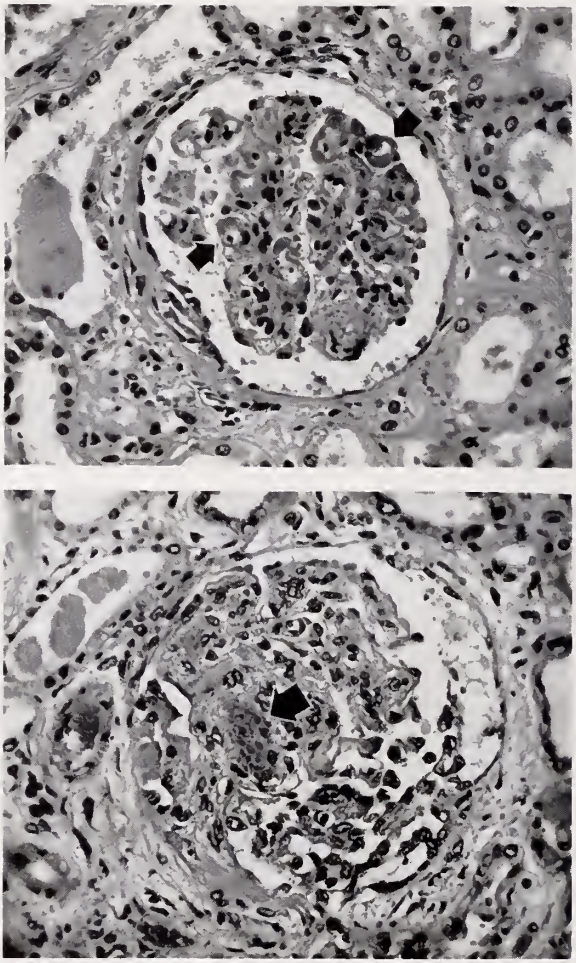


FIG. 1. Glomerulus from autopsy case (not treated with steroids). Note several thick wire loop lesions (arrows) and minimal inflammatory changes. Hematoxylin and eosin, × 375.

FIG. 2. Glomerulus from autopsy case (treated with steroids). Note cellular proliferation, crescent formation, and area of necrosis and hemorrhage (arrow). No noticeable wire loops. Hematoxylin and eosin, × 375.

In the more advanced stage of the disease, the basement membrane often split into two or more layers, with deposition of the granular material between the layers (Fig. 4). This corresponded to the fully developed "wire loop" lesion of light microscopy. Splitting was eventually followed by breaks in the outer layer. The broken fragments projected towards the epithelial cells producing a tooth-

like appearance ("membranous transformation"). The granular material occurred not only between the layers of the split membrane, but also under the endothelium and under the epithelium. Sometimes the deposit extended from

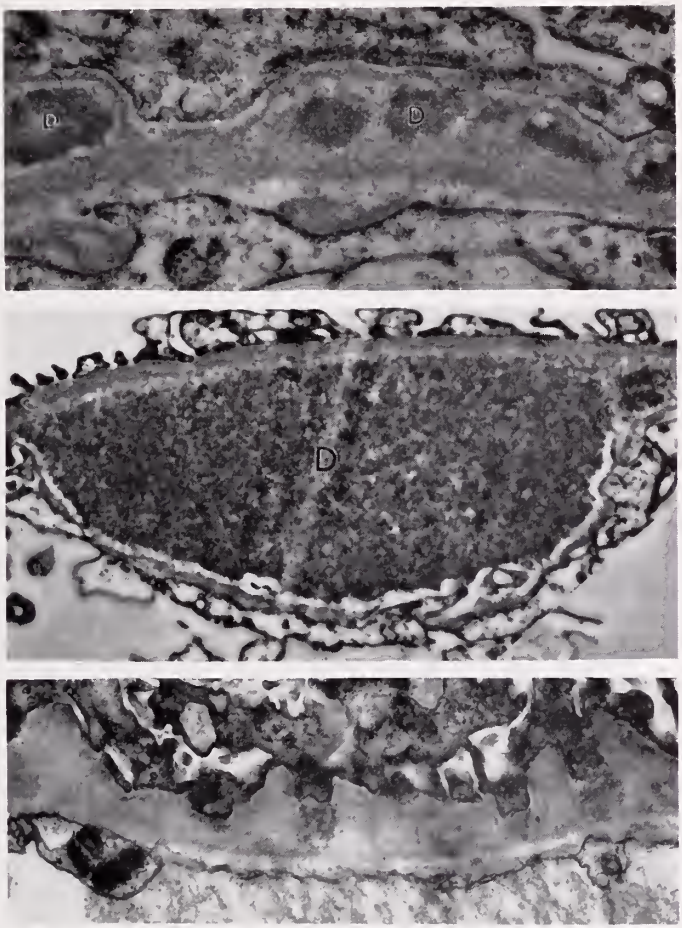


Fig. 3. Part of glomerular capillary wall; urinary space at top, capillary lumen at bottom; epithelial foot processes fused; thickened and split basement membrane with dark deposits (D) between layers. Electron micrograph, × 25,000.

Fig. 4. Wall of glomerular capillary. Thickening and splitting of basement membrane with massive deposit of dark granular material (D) between split layers ("wire loop"). Electron micrograph, × 10,000.

Fig. 5. Portion of glomerular capillary. Irregular thickening and spike formation of basement membrane ("membranous transformation"). Electron micrograph, × 18,000.

the endothelium to the epithelium, causing a break in the continuity of the basement membrane (Fig. 6).

Swelling of endothelial cells, with bleb formation, often resulted in narrowing of the capillary lumen. Swelling and vacuolation of epithelial cells were usually present, together with variable fusion and distortion of foot processes.

The intercapillary space was widened and contained an increased number of cells. Thin-section light microscopy showed fiber-like and proteinaceous materials in this area (Fig. 7). In the electron microscope these fibers were of the same

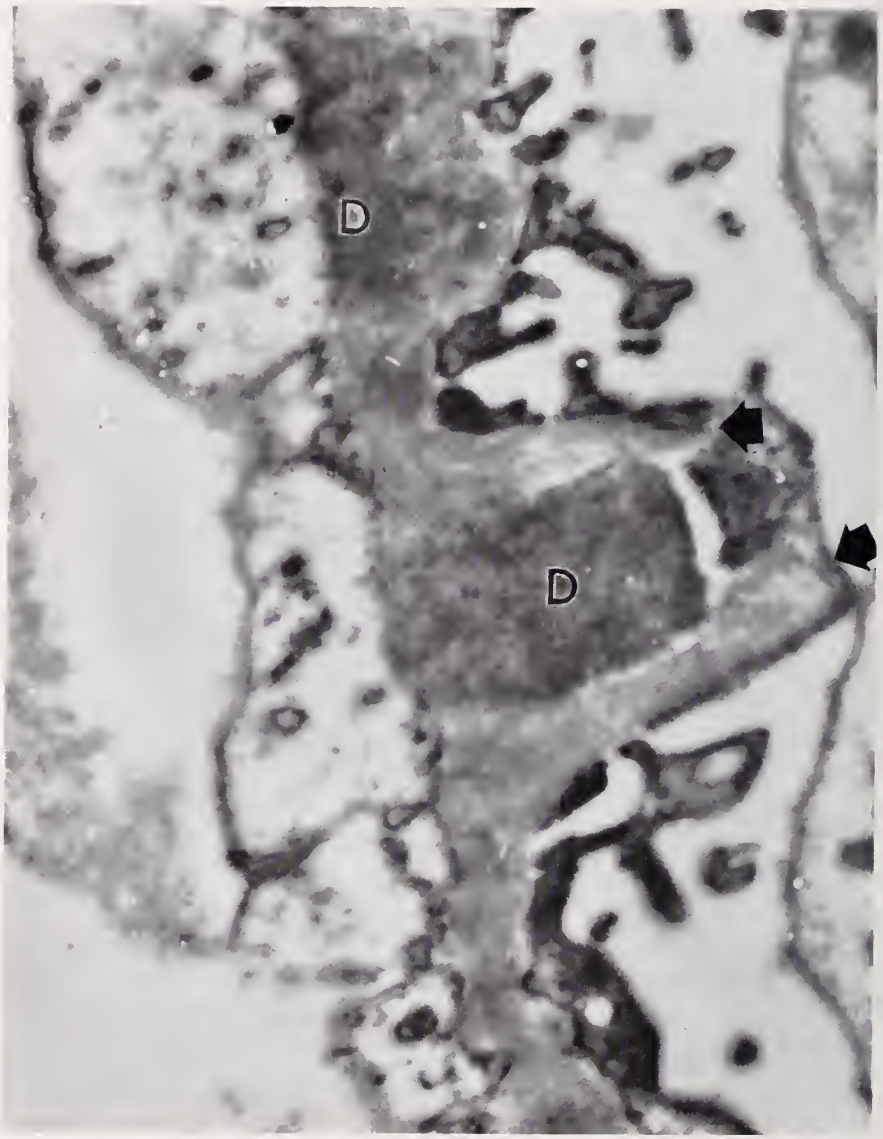
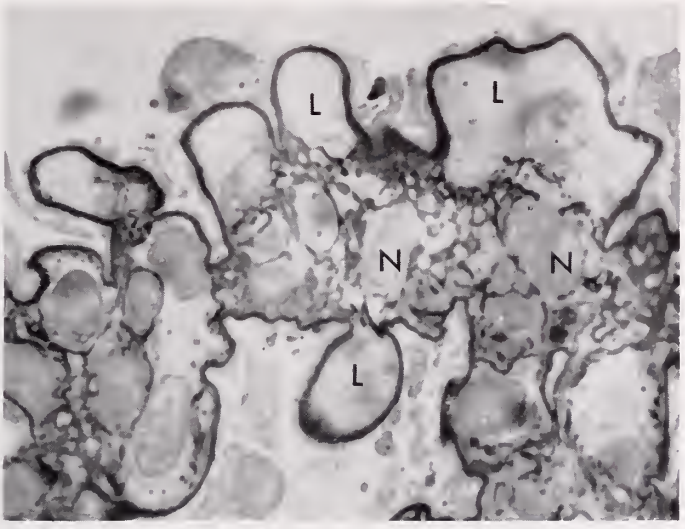


FIG. 6. Portion of capillary wall with thickening of basement membranes and deposits; large deposit in center extends from the edematous endothelium to the epithelium, causing a break in the basement membrane; both ends of the broken membrane project perpendicularly towards the urinary space (arrows). Electron micrograph, × 25,000.

density as the capillary basement membrane, from which they seemed to branch. The branches extended between the intercapillary cells, occasionally encroaching on their cytoplasm. Frequently they were associated with electron-dense granu-

lar deposits, similar to those along the basement membrane of the capillary walls (Fig. 9). With progressing disease the fibrous structures increased and the number of cells decreased in the intercapillary space and there was deposition of collagen (Fig. 8). Finally, capillary compression or collapse led to obsolescence of glomeruli.



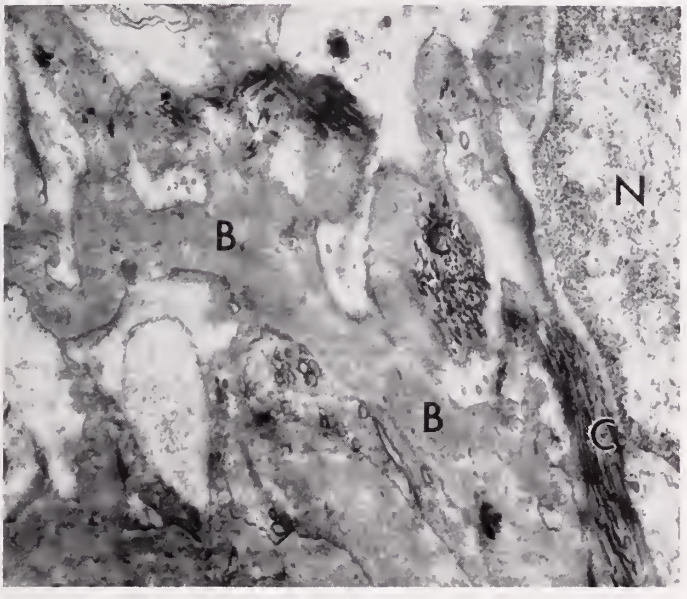


FIG. 7. Glomerular lobule with markedly widened intercapillary space surrounded by open capillaries (L); space contains pale staining intercapillary cells (N) and tangled basement membrane branches. Light micrograph, thin section, PAS, × 3,000.

FIG. 8. Portion of intercapillary space showing intercapillary cell with nucleus (N) at right, basement membrane branches (B), and darkly stained collagen (C). Phosphotungstic acid stain. Electron micrograph, × 15,000.

In addition to the changes just described, some glomeruli showed focal necrosis of tufts, hematoxylin bodies, and capillary thrombosis. Because of their scarcity these lesions proved difficult to study by electron microscopy. One area of fibrin-

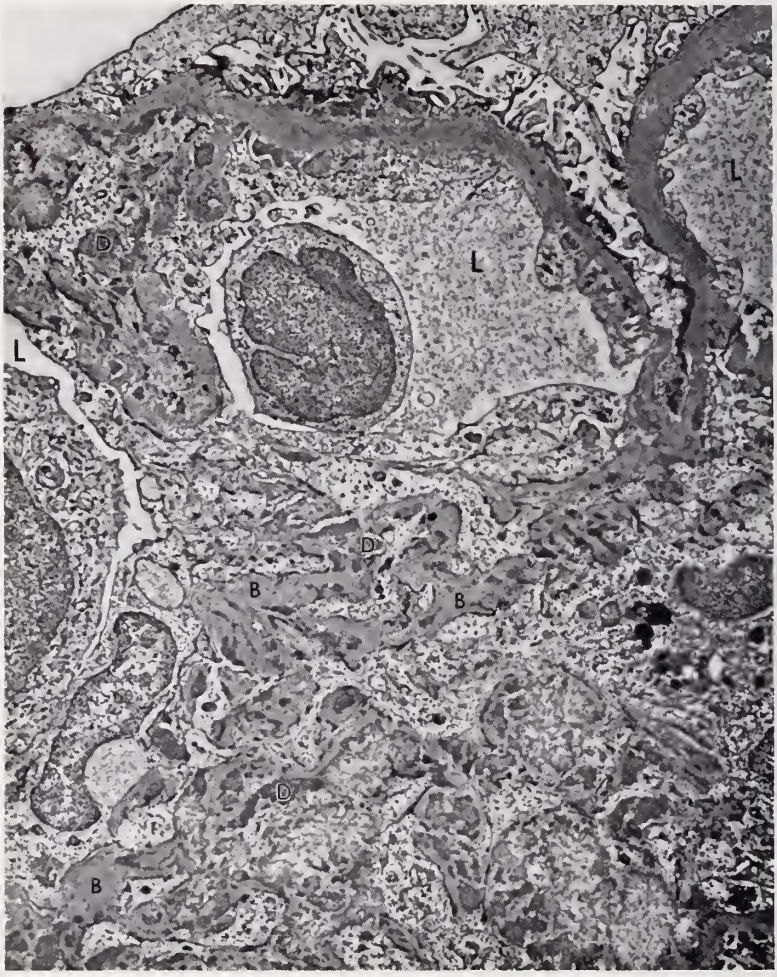


FIG. 9. Glomerular capillaries (top) (L) and intercapillary space (bottom). Note many basement membrane branches (B) in intercapillary space associated with dark, granular deposits (D). Electron micrograph, × 12,500.

oid necrosis revealed a mass of cells of unknown nature surrounded by homogeneous, dark gray material. This apparently corresponded to the "fibrinoid" seen in light microscopy. The basement membrane seemed to end abruptly within the cell mass. Neighboring epithelial cells contained large, spherical hyaline droplets.

The changes in the tubules and intertubular stroma were those usually associated with glomerular damage—tubular atrophy, interstitial fibrosis, and in-

flammation. Fibrinoid necrosis of the walls of small arteries roughly paralleled the focal necrosis of glomeruli.

Of the 20 biopsied cases, 7 were also studied postmortem. The interval between biopsy and autopsy ranged from a few days to two years. As might be expected, the pathologic features of the autopsy specimens obtained soon after the biopsy differed only slightly from those of the biopsy material, except for differences which could be attributed to the much larger amount of tissue available for examination. With longer intervals between the two examinations, there was a greater percentage of obsolete glomeruli, and the disease was in a more advanced stage. Basement membrane thickening and glomerular and arteriolar necrosis were more prominent, and hematoxylin bodies were more frequent. The number of wire loop lesions seemed to be about the same. In general, the autopsy material showed slight or moderate progression of the disease.

Autopsy material

In addition to the 7 cases just mentioned, 18 others were studied postmortem. Of these 25 patients, 14 had received steroid therapy, 11 had not. The patients in the first group had survived for a number of years (average 2.8 years), those in the second had generally died during an acute attack of the disease (average 1.6 years). In the nontreated group the obsolete glomeruli amounted at most to ten per cent, the disease process was in a relatively early stage, and inflammatory and proliferative changes in the glomeruli and intertubular stroma were mild; wire loops were present in every case, in some instances involving most of the glomeruli (Fig. 1). Eight cases showed necrosis of glomerular loops, usually accompanied by fibrinoid deposits in small arteries. Hematoxylin bodies were found in 7 cases.

In the steroid-treated group, the disease was more advanced: up to ninety per cent of glomeruli were obsolete (average 25%), and considerable nonspecific inflammatory and proliferative changes were present (Fig. 2). Wire loops were few and in ⅓ of the cases were completely absent. Hematoxylin bodies were rare (4 out of 13 cases); necrotic areas, though, were comparatively common (10 cases). Fibrinoid necrosis of small arteries was seen only in a few cases, while arteriosclerosis and arteriolosclerosis were more prominent.

DISCUSSION

Muehrcke and co-workers (1), who have described the histopathology of lupus nephritis as seen in renal biopsy material by light microscopy, confirmed the autopsy findings of Klemperer and co-workers (2). Farquhar, Vernier and Good (9) were the first to describe the electron microscopic features of this disease. Various specific and nonspecific changes have been found in lupus nephritis. Among the specific features are hematoxylin bodies, and to a degree, wire loop lesions, and focal necrosis of glomerular capillary loops. Cellular proliferation and inflammatory changes are nonspecific.

Electron microscopy demonstrates thickening and splitting of the capillary basement membrane, increase in number of intercapillary branches, and deposi-

tion of electron dense granular material. These changes appear to be closely related, though it is not yet clear whether deposits or changes in the basement membrane appear first. The fully developed "wire loop" of light microscopists embraces both these changes.

Several other diseases, in which changes in glomerular basement membrane and proteinaceous deposits occur, must be differentiated from lupus nephritis (10). In diabetic glomerulosclerosis, the basement membrane thickens long before the electron dense material is deposited, the latter process occurring only in the so-called exudative phase of the disease. In late acute and in subacute glomerulonephritis, there may be deposits of electron-dense material within the capillary wall, but they are much smaller quantitatively and are located mainly on the outer surfaces of the capillary basement membrane. The so-called membranous glomerulonephritis is characterized by perpendicular spikes of the basement membrane, with deposits between the spikes and the epithelial cells. Large glomerular deposits are also found in toxemia of pregnancy, but the material is located between the endothelial cells and the basement membrane (11).

The important role of the intercapillary space in glomerular disease has been emphasized by Jones (12) and by others (13–16). The normal space contains a few cells and branches of basement membrane, and is separated from the capillary lumens by incomplete, delicate membranes. In systemic lupus erythematosus, the space is often widened as a result of excessive membrane formation and deposition of electron dense material. These changes are similar to those in the capillary walls and could be regarded as another manifestation of the same process.

Smith (17) has suggested that the structure of the eosinophilic material in the glomerular focal necrosis resembles that of the wire loop material, but our observations do not confirm this; the wire loop material is of coarsely granular structure, whereas the necrotic material is considerably more homogeneous. Focal necrosis often caused adhesions between capillary tufts and Bowman's capsule; healed areas of necrosis had the appearance of fibrous nodules.

Freedman eluted the material deposited along the basement membrane of a kidney from a case of lupus nephritis; he suggested that it may be of antibody nature, since it contains gamma-globulin and complement (18). The eluted substance combined with nuclei of normal kidney, as well as with nuclei and capillary wall tissue of the diseased kidney. Various antibodies have been found in the serum of patients with systemic lupus (19); some of the antibodies are antinuclear, others react with various cellular components. Possibly, the wire loop material is an antibody against basement membrane and its branches. It may also be an antigen-antibody complex or some other abnormal protein trapped in the basement membrane, or perhaps even that of a local degenerative change of the membrane.

The nonspecific changes of lupus nephritis consist of cellular proliferation and chronic inflammation. These changes appear later in the disease, perhaps as a reaction to the damage of capillary walls and intercapillary spaces. The more advanced stages of lupus nephritis closely resemble those of chronic glomerulonephritis, but the evolution of the lesion in the former is quite different, since the

picture of acute glomerulonephritis is not seen in lupus nephritis. There is some resemblance between lupus nephritis and the type II nephritis of Ellis (20) which he described as a progressive glomerular hyalinization involving the intercapillary stroma and basement membrane, and leading to diffuse renal destruction. The term "lupus nephritis" has been widely accepted although it is actually a slowly progressive form of basement membrane damage, with the associated inflammatory changes probably constituting a secondary manifestation.

The histologic features of biopsy and autopsy specimens from steroid treated cases differ considerably from those before the introduction of steroid therapy, a change also emphasized by Muehrcke and co-workers (1). It appears that steroid treatment suppresses the "specific" renal changes, such as "wire loop" lesions and hematoxylin bodies. However, in the dosages usually employed, they do not inhibit progression of the inflammatory and proliferative changes. Though the patients live longer, most of them eventually succumb to obliterative disease of the glomeruli (21). Recently Pirani and co-workers reported that prolonged treatment with large doses of prednisone appears to control the "active" lesions of lupus nephritis and to slow down the progression of the renal lesion (6).

SUMMARY AND CONCLUSIONS

Standard and thin-section light microscopy and electron microscopy were used to study the histopathologic features of lupus nephritis in a series of 38 cases, of which 27 had been treated with steroids. Renal biopsy was performed in 20, and 7 of these were followed by study at autopsy.

Standard light microscopy revealed various combinations of nonspecific inflammatory changes with more specific features, such as focal necrosis, wire loop formation, and hematoxylin bodies. Thin (0.5 micron) sections were useful for detecting small deposits along the basement membrane ("micro-wire loops"), breaks in the basement membrane, and changes in the intercapillary spaces.

In biopsy specimens, electron microscopy showed thickened capillary basement membranes and associated deposits of electron-dense granular material within and around the basement membrane, occasionally causing breaks in its continuity. The deposits are believed to be identical with the wire loop material seen on light microscopy. The intercapillary spaces were widened by cellular proliferation, a marked increase in basement membrane branches, and granular deposits in and around the branches. It is believed that the combination of changes in the capillary walls and intercapillary spaces is characteristic for systemic lupus erythematosus.

Steroid therapy, in the dosages employed, tended to decrease the intensity of the specific glomerular changes in lupus nephritis, such as formation of wire loops and hematoxylin bodies, but did not affect the progress of the nonspecific inflammatory and fibrotic changes.

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Percutaneous Brachial Vertebral Arteriography

A Simplified Technique for Intracranial Visualization*

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Since its popularization in Scandinavia, the original Seldinger technique for percutaneous arterial catheterization has gained widespread use (1). In 1959 Pygott and Hutton (2) and, by 1960, Begg (3) and Elfvin (4) reported on their adoption of this technique for neuroradiologic purposes. Few, if any, major modifications in the technique have been described prior to the recent communication of Tatelman and Sheehan (5).

This method was undertaken because of dissatisfaction with certain aspects of the direct percutaneous vertebral puncture, which had been the standard approach to vertebral arteriography at The Mount Sinai Hospital (6–9). Direct vertebral puncture is usually painful for the patient, often difficult for the physician to perform and does not ordinarily (10) visualize the entire vertebral artery. Even when the initial puncture is easily accomplished, there is often difficulty keeping the point of the needle in the lumen of the vessel long enough to obtain a complete study; this problem is magnified when the patient is uncooperative or when the X-ray equipment available necessitates changing the position of the patient's head and neck during the procedure. General anesthesia, which eliminates the problem of patient cooperation, has not generally been employed because of increased risk to the patient, and elimination of subjective responses which are often useful in determining whether the injection is entirely intraluminal.

In the series being reported here, the Seldinger technique was again employed but was modified with maximum technical simplicity as a major objective. Percutaneous introduction of the catheter over a flexible spring wire guide, eliminating the need for surgical arteriotomy or sacrifice of an arterial vessel, was maintained as the basis of the procedure (11). The technique was simplified by: 1) substitution of standard polyethylene tubing which is not radiopaque, 2) elimination of fluoroscopic control and 3) avoidance of the need for an automatic or high pressure injecting device.

Adequate intracranial vertebro-basilar arteriograms can be obtained by this method in a percentage of cases which compares favorably to that obtainable by the direct percutaneous vertebral puncture method. The opacification of intracranial vessels may be equivalent, somewhat less dense or, in many cases, superior by the catheterization technique. Often on the right side, there is simultaneous visualization of the carotid system. The procedure is easier for the physician to perform, less painful for the patient than the direct percutaneous

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† This study was carried out while the authors were trainees under a USPHS Grant.

vertebral puncture method and remains available even after direct puncture attempt does not produce adequate films for any reason. In addition it demonstrates the proximal portion of the vertebral artery and its origin from the subclavian artery which are not ordinarily visualized by conventional direct puncture. This technique can also be used for demonstration and, possibly, for therapeutic perfusion of other branches of the parent vessel, *e.g.* internal mammary artery and thyrocervical trunk.

MATERIAL

Eighty-six successful percutaneous brachial catheterizations were performed for the primary purpose of vertebral arteriography. Early in the series there were several unsuccessful attempts at catheterization; the last 73 consecutive attempts succeeded.

METHOD

The patient is premedicated with atropine and 2 to 3 grains of a barbiturate administered by the intramuscular route. The last 35 patients received 160 mg of Papaverine® intramuscularly.

The choice of the arm employed is generally arbitrary unless it is specifically desired to demonstrate one vertebral artery in its cervical portion. Among the other factors which limit this choice in some cases are: 1) certain suggestive clinical entities such as infarction of the dorsolateral wedge of the medulla; 2) recent trauma to a vertebral artery as results from percutaneous vertebral arteriography and 3) local problems related to the accessibility and course of the brachial artery.

With the patient lying supine the arm is extended at the elbow and abducted at the shoulder. The brachial artery is palpated in the antecubital fossa; the forearm is positioned in pronation or supination, whichever makes the vessel more prominent. A blood pressure cuff is placed on the upper arm and the antecubital region is cleansed with 70 per cent alcohol. The arm is draped with sterile towels. The skin is infiltrated with procaine and a tiny skin incision approximately ⅛ inch in length is made to facilitate passage of the catheter through the skin. A #11 Bard Parker blade is used for this purpose. A 36-inch length of clear polyethylene catheter* is then prepared in the following manner. A short length of flexible wire spring guide† is introduced into one end of the catheter. The catheter end with the short length of guide protruding is warmed over an alcohol flame while rolling it back and forth between the thumb and forefinger of each hand; slight tension is applied. The catheter soon stretches forming a tapered segment. When selective catheterization of the vertebral artery is desired, the catheter is immediately bent into a "U" and allowed to cool for several seconds. The guide is then removed and the catheter is cut with a scissor along the tapered segment in the shape of a "J"; the resulting curvature should

* Sterile prepackaged Clay-Adams PE 205/S36.

† Syracuse Spring Corp., "catheter guide wire" 0.046 inches outer diameter.

be between 45 and 90 degrees. If selective catheterization is not to be attempted the straight tapered segment is cut so that the catheter fits loosely over the guide. The unprepared end of the catheter is now cut to 21-inch length.

The 26-inch wire spring guide is laid out and its inner stiffener wire is withdrawn one inch so as to leave the proximal inch of guide more flexible.

The brachial artery is punctured in the usual manner of carotid artery punctures using a 16-gauge thin-walled Cournand needle.* Once excellent flow has been obtained the needle is threaded at least ¾ inch up the artery. The guide is then inserted through the needle into the lumen of the artery for 3 to 5 inches. The blood pressure cuff is inflated above systolic pressure to maintain hemostasis and the needle is then withdrawn while the guide is held stationary. During the usual five minute period of hemostasis, the needle is completely removed from the guide and the guide is cleared of any blood; the catheter is then threaded over the guide up to the skin hole. The cuff is deflated; the guide and catheter are advanced as a unit with a slight twisting movement into the artery and are passed for a predetermined distance, usually 14 to 19 inches. This distance is based upon an external measurement from the skin hole on a straight line to the ipsilateral border of the trachea. The guide is then rapidly withdrawn and a Luer stub adapter fitted to the free end of the catheter. The catheter is flushed with citrated saline and taped to the skin.

To determine the position of the tip of the catheter, a single scout film centered over the ipsilateral sternoclavicular joint is taken while 50% Hypaque® is injected very slowly (approximately one cc/second). A considerable amount of time can be saved if Polaroid film is used. An examination of this film reveals whether the tip of the catheter is in the parent vessel (innominate and/or subclavian) or whether it has fortuitously entered a branch vessel (thyrocervical trunk or vertebral artery). If it is in the vertebral artery as in Figure 1 intracranial serial arteriography may proceed. In the former case only the catheter will be opacified and a second film (Figs. 2, 3) using a forceful injection of 10 cc of 50% Hypaque® is taken; during this injection the cuff may be inflated above systolic pressure to decrease run-off of contrast medium down the brachial artery; this film usually opacifies the innominate, subclavian, internal mammary, thyrocervical and, in particular, the point of origin of the vertebral artery. From these two films the distance between the tip of the catheter and the origin of the vertebral artery can be measured with considerable accuracy. The catheter may then be advanced or withdrawn to a desired position. Adequate intracranial filling of the vertebro-basilar system can, in most cases, be obtained when the catheter tip is ½ to 1 inch distal to the vertebral orifice. If demonstration of the right carotid circulation is desired the catheter tip should be advanced one or two inches. If selective catheterization is desired the catheter tip should be withdrawn to approximately ⅛ inch distal to the orifice of the vertebral artery and then the catheter should be slowly advanced.

When the catheter tip is in the subclavian artery distal to the vertebral orifice

* Manufactured upon request by the Becton, Dickinson Co.

FIG. 1. Slow injection (1 cc/sec.) Catheter tip in vertebral artery.

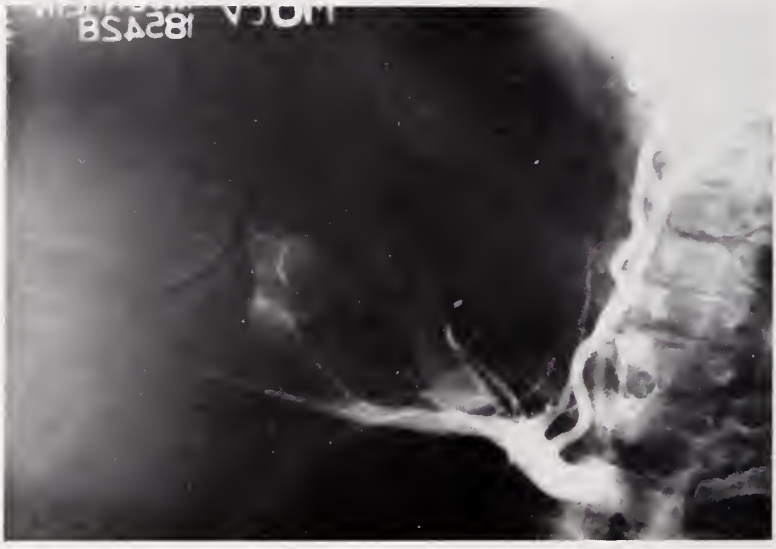

FIG. 2. Forceful 10 cc injection. Right innominate and carotid system faintly opacified; right subclavian, vertebral, thyrocervical trunk and branches densely opacified.

we have used hand injection of 20 to 25 cc of 50% Hypaque® for intracranial serial arteriography; when the catheter tip is in the vertebral artery hand injection of 6 to 10 cc of 50% Hypaque® suffices.

After the desired films have been obtained the catheter is withdrawn and the blood pressure cuff immediately inflated above systolic pressure for 5 to 8 min-

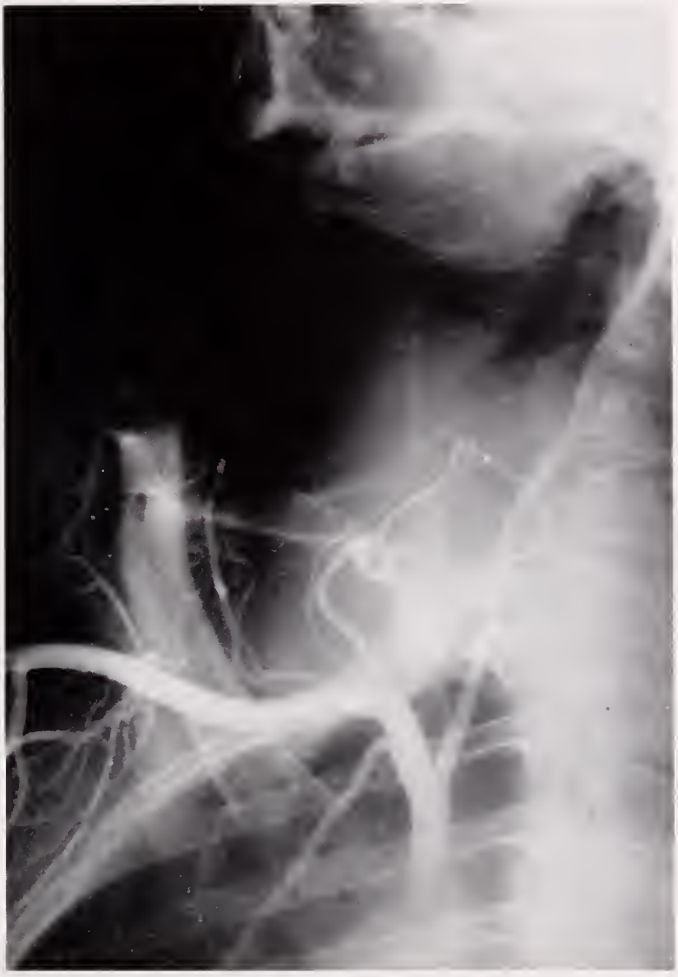

Fig. 3. Forceful 10 cc injection, opacifying left subclavian, vertebral, internal mammary, thyrocervical trunk and other branches.

utes. The cuff is then slowly deflated; if bleeding occurs, manual compression for 2 to 3 minutes usually suffices.

RESULTS

1. Eighty-six successful percutaneous brachial catheterizations were performed for vertebral arteriography. The films were first evaluated in terms of density of intracranial filling:

Density of Intracranial Filling

Excellent	54
Adequate	15
Poor (include no filling)	17

Of the 17 patients whose intracranial vasculature was not visualized, two had vertebral artery occlusions; 11 had excellent filling of the vertebral artery in the neck but little or no intracranial filling. Analysis of this group of cases as differentiated from clear-cut vertebral occlusions is the subject of another article in this journal (27). This article suggests that spasm of the vertebro-basilar artery system occurs with considerable frequency during arteriography.

Of the remaining four studies in which intracranial filling was not obtained, in one case the catheter could not be advanced more than several inches due to tortuosity and atherosclerosis of the brachial artery; in another case the configuration of the thyrocervical trunk prevented advancement of the catheter beyond a point more than two inches distal to the vertebral orifice; in the third case (Fig. 4) an anomalous (right) subclavian artery was demonstrated arising from the descending aorta; no vertebral artery arose from this vessel; in the fourth case the vertebral artery had an extremely small calibre.

2. Of the 86 brachial catheterizations, 66 were performed on the right side and 20 on the left side. When the catheter tip was in the right subclavian artery, excellent or adequate intracranial filling of the right carotid circulation (Figs. 5, 6) was obtained inadvertently in sixty per cent of the cases; excellent intracranial filling was obtained in all cases in which it was desired.

3. Selective catheterization of the vertebral artery has been a specific goal in the last 39 cases and was achieved with minimum difficulty in 19 cases (Figs. 7, 8). The chances for success of selective catheterization seem to improve with experience.

4. Inadvertent catheterization of the thyrocervical trunk occurred in 23 cases. In most cases the catheter could be withdrawn and then readvanced beyond this vessel orifice. It should be noted that in most patients the thyrocervical trunk originates so close to the vertebral artery that the catheter tip is in the desired position, *i.e.*, less than one inch distal to the vertebral artery orifice, even though it cannot be advanced beyond the thyrocervical trunk. Other vessels of the upper arm and shoulder were entered on two occasions.

5. In 32 cases either pathology or congenital anomaly was demonstrated. (Figs. 9, 10).

COMPLICATIONS

1. Minor: Minor complications included (A) Local ecchymosis in the region of the brachial artery puncture; this was quite common. (B) in approximately half the patients the forcefulness of the radial pulse determined by palpation was transiently somewhat diminished. In four cases the radial pulse was absent for several days but subsequently returned. At no time in any patient were there signs or symptoms of arterial insufficiency of the arm. Oscillometry was per-

formed in a small number of patients. There was poor correlation between the strength of the pulse and oscillometric readings. (C) delayed arterial bleeding following termination of the procedure has not occurred. (D) generalized sei-

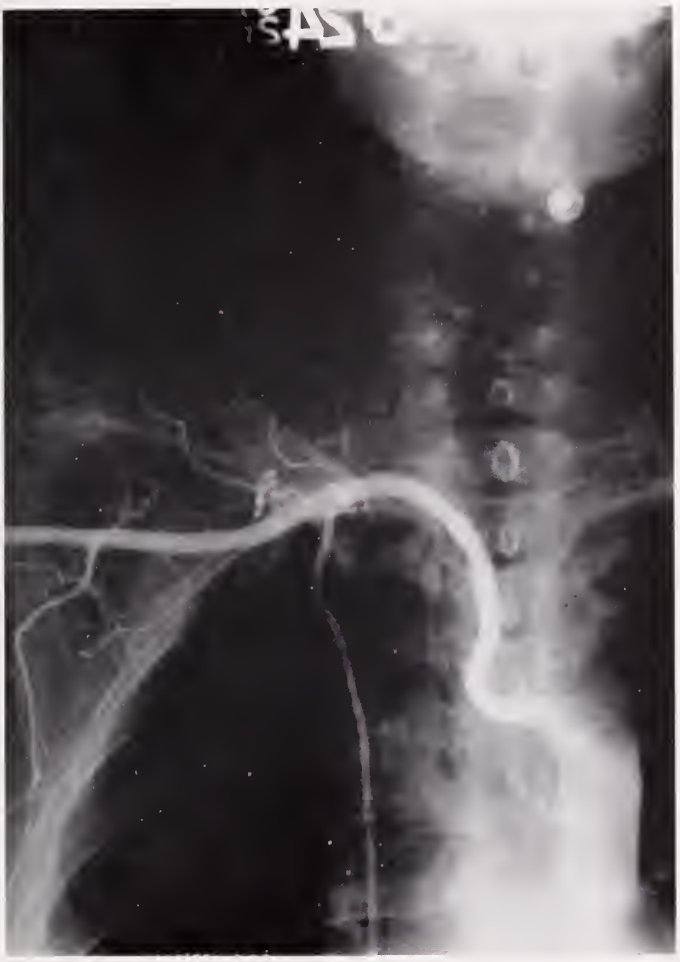

FIG. 4. Anomalous right subclavian artery arising from descending aorta. No vertebral artery could be demonstrated arising from this vessel. Note good opacification of its other usual branches.

zures occurred in two cases, with onset during the latter part of the Hypaque® injection.

2. Major: There were no major complications. There was no instance of worsening of the neurological condition of the patient directly attributable to the arteriographic procedure; there were no cases of blindness or quadriparesis. There were no signs or symptoms of brachial artery insufficiency.

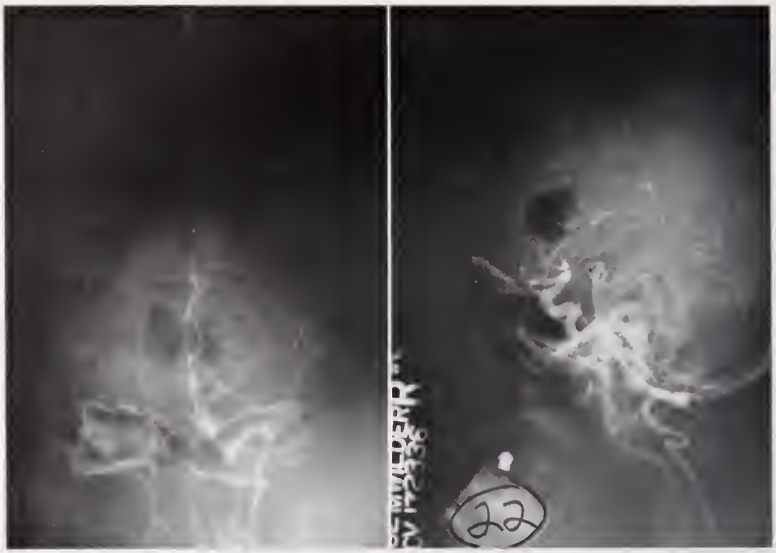

FIG. 5. Frontal projection. Simultaneous opacification of right carotid and vertebral systems. Opacification classified as "adequate."

FIG. 6. Lateral projection. Same as Fig. 5.

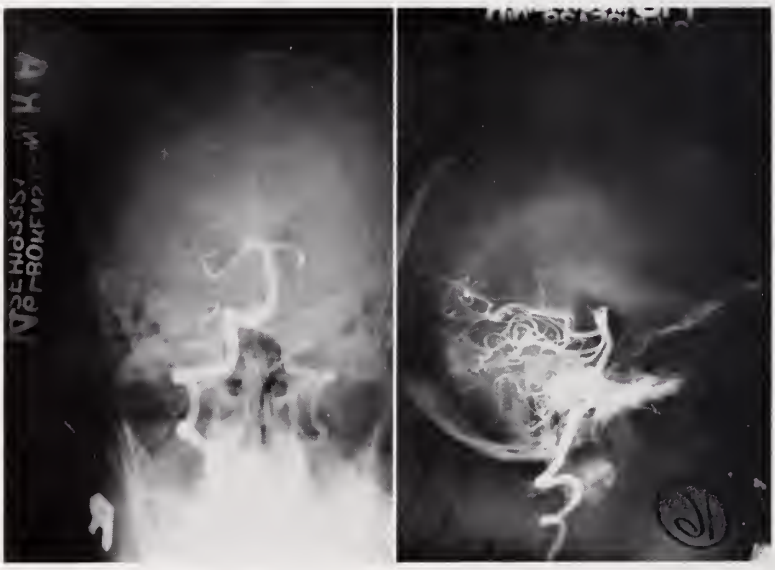

FIG. 7. Frontal projection. Catheter in vertebral artery.

FIG. 8. Lateral projection. Catheter in vertebral artery.

DISCUSSION

Numerous methods have been described for vertebral arteriography. The direct percutaneous vertebral puncture method (7, 9) is technically difficult, often painful and has a high rate of complications; these include blindness (8), the

development of arteriovenous fistula in the neck (12) and brachial plexus injury (13). In addition this technique does not give information about the status of the proximal portion of the vertebral artery unless special equipment is used (10).

The direct percutaneous subclavian puncture method (14–16) has been reported to have a significant incidence of pneumothorax and, occasionally, hemothorax (17). This seems to be true whether the approach be supraclavicular or infraclavicular. In addition an instance of necrosis of the cervical spinal cord has been reported following arteriography by this technique (18). A causal relationship is by no means obvious, however. Finally, the distance between the needle tip and the vertebral orifice must remain relatively constant even though

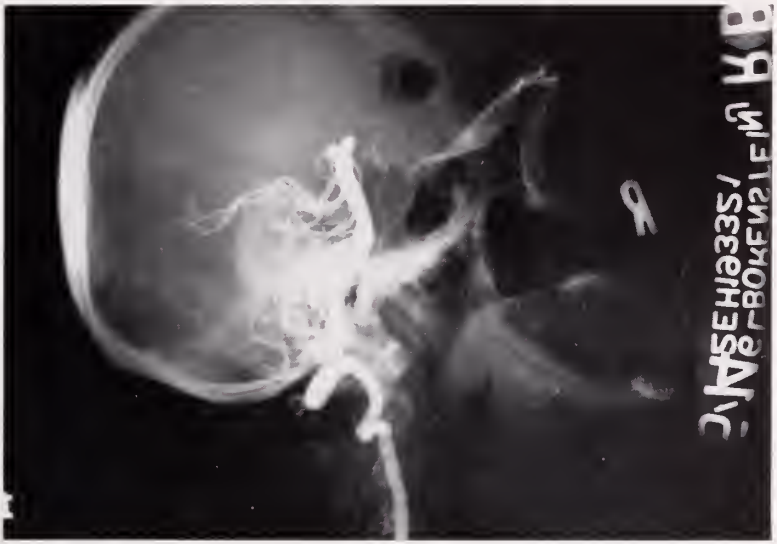

FIG. 9. Ectasia of basilar artery. This corresponded to a smooth defect in the floor of the third ventricle demonstrated by pneumoencephalography.

the vertebral orifice may be discovered to be in an unexpected position. As in all procedures utilizing a needle alone there is a greater likelihood that an uncooperative patient may dislodge the needle.

The method of direct retrograde injection through a needle at the antecubital fossa or more proximal brachial artery (19, 20) carries with it the usual disadvantages of using a needle alone in addition to the risk added by the use of a high pressure injection device (21), often with larger quantities of contrast material. The predictability of intracranial filling is poor.

The method of retrograde injection of the right common carotid artery (22, 23) with simultaneous right carotid and brachial artery compression is also unpredictable.

Femoral catheterization using the Seldinger technique (6, 24) may have three unique risks. The collateral circulation of the lower extremity is said to be more tenuous than that of the upper extremity (25) and the major vessels are proba-

bly more frequently involved by disease processes. Second, late arterial bleeding occurs following femoral punctures but is extremely rare following brachial punctures (25). In addition, there is the possibility that an unsuspected aortic aneurysm might be encountered and damaged during the catheterization.

The intravenous approach requires surgical phlebotomy, large, often bilateral

Fig. 10. Congenital anomaly of basilar artery.

simultaneous contrast injections under high pressure and frequently yields inadequate intracranial filling (26).

Brachial catheterization remains the safest and one of the least painful methods for vertebral arteriography; it gives information about the entire vessel including its origin (5). It allows for that flexibility in technique needed for optimal catheter placement to produce densest intracranial filling. The modifications of the Seldinger technique presented here eliminate the need for radiopaque tubing.

fluoroscopy, high pressure fittings and injection devices. The procedure does not take significantly longer to perform than any of the other described methods, particularly when Polaroid techniques are used. Significant complications are apparently so rare that in 86 consecutive studies none has occurred. Minor complications such as local ecchymoses and decrease in the forcefulness of the

FIG. 11. Kink and constriction at origin of dilated vertebral artery.

radial pulse were frequent but not significant. This complication rate is substantially the same as that reported by Tatelman and Sheehan in their recent series of 220 cases (5).

SUMMARY

1. In a series of 86 brachial catheterizations for vertebral arteriography, adequate intracranial studies were obtained in 69 cases and vertebral occlusion was proved in 2 cases. In 11 of the remaining 15 cases the evidence suggests

that spasm of the vertebro-basilar system occurs during the injection of Hypaque®.

2. A technique of percutaneous brachial catheterization and subsequent catheter arteriography of the vertebral artery is described; this technique is safe, easier, less painful and gives more information than the direct vertebral artery puncture technique.

3. Representative arteriographic studies are presented.

4. No major complications have occurred.

ACKNOWLEDGMENT

The authors are indebted to the Department of Radiology of The Mount Sinai Hospital.

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Vertebral Artery Spasm During Arteriography*

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In a series of 86 consecutive vertebral arteriograms obtained by retrograde brachial catheterization the basilar artery was not visualized in 16 studies, but in none of these was there true occlusion (1). From 11 of these 16 cases there emerged a constant pattern which distinguished such lack of visualization from true occlusive disease of the vertebral and basilar arteries at various levels. This paper suggests that the "apparent occlusion" of the vertebral artery was functional in nature.

RESULTS

In the 86 studies performed, there were 6 examples in which obstruction was proved to be transient and 5 studies in which this pattern was suggested but absolute criteria were not fulfilled.

1. The site of apparent obstruction was at the vertebro-basilar junction in 10 and at multiple cervical levels in 4 studies. In 3 cases the apparent obstruction was at both sites during a single study.

2. This pattern of obstruction occurred nine times in right-sided studies and twice with left-sided studies; this is not significantly different from the ratio of right to left studies performed.

3. Obstruction proved to be transient was encountered in 3 of 19 studies when the catheter had been introduced into the vertebral artery itself and occurred in 3 of 67 studies when the catheter tip was in the subclavian artery. Of the remaining (suggestive) studies, the catheter tip was in the vertebral artery in 3 and in the subclavian artery in 2.

4. Although inadequate intracranial studies were first obtained in 6 of the cases in which the catheter was in the vertebral artery, adequate studies were eventually obtained in 3. In the 5 cases in which the catheter was in the subclavian artery inadequate intracranial filling persisted in all 5.

5. 160 mg of Papaverine® was given intramuscularly to 35 patients prior to their study; no Papaverine® was given to 51 patients. The pattern described developed in 5 patients of the former group and 6 patients of the latter group. This does not appear to be a significant difference.

6. Intra-arterial Papaverine® was given to 3 of the 6 patients in whom the catheter was in the vertebral artery when the aforementioned pattern developed. In 2 of the 3 patients given intra-arterial Papaverine® reversal of the apparent occlusion followed. Spontaneous reversal did not occur in the other 3 patients.

* This work was performed while the authors were trainees under USPHS Grant 478.

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RADIOGRAPHIC FEATURES

The eleven cases under consideration can be subdivided into two groups according to the level of the vertebral artery at which the apparent occlusion is demonstrated. In the six proved cases it was demonstrated that this occlusion

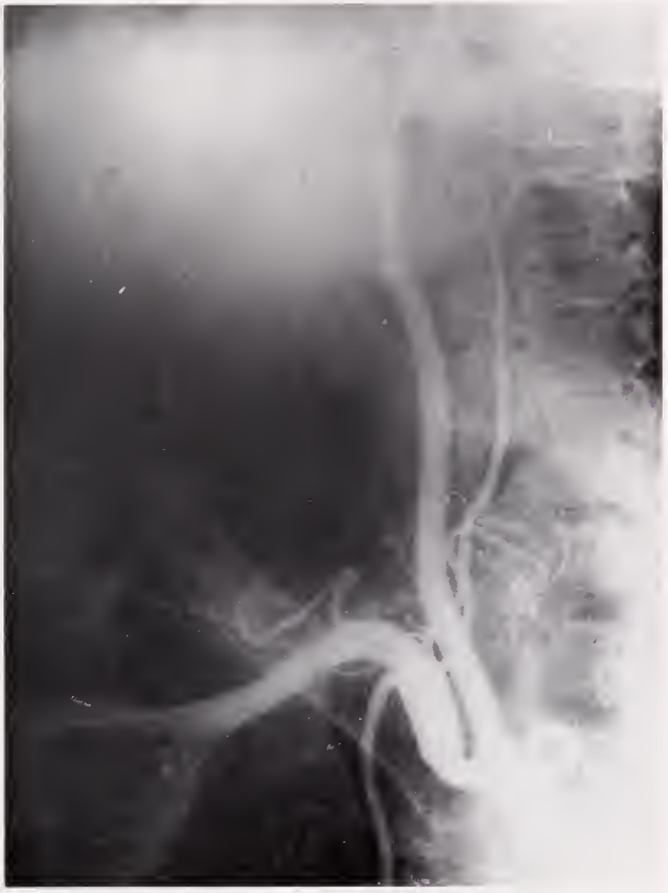

FIG. 1. Case 1. Catheter in right subclavian artery. Vertebral well filled. Previous films had demonstrated apparent obstructions at C5–7 region.

was not constant, being present during one but not another (usually subsequent) portion of an arterial study nor at postmortem examination.

1. Cervical Levels

In the following cases the vertebral artery was well filled with contrast material up to a point which could have been interpreted as the site of an occlusion had not prior or subsequent injections revealed completely normal filling or a block at a different level.

CASE 1

Right brachial arteriogram. Hand injection was made with the catheter tip in the right subclavian artery somewhat distal to the vertebral orifice. Successive films revealed several different levels of obstruction to the cephalad flow of contrast material in the lower cervical region. On the last injection, however, the entire vertebral artery could be seen (Fig. 1), thus proving that the previous "occlusive" defects were transient.

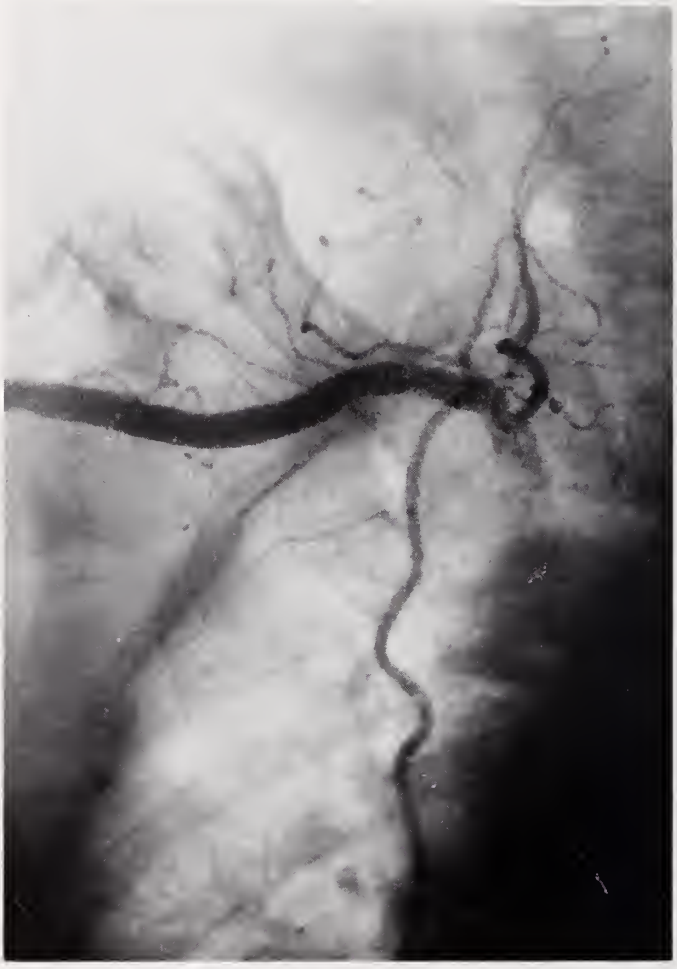

FIG. 2. Case 2. Catheter in left subclavian artery. Late film with 10 ml contrast reveals no vertebral filling above C5–6 region; all other vessels are already well filled to their distal branches.

CASE 2

Left brachial arteriogram. Hand injection was made with the catheter tip in the left subclavian artery somewhat distal to the vertebral orifice. Successive scout films revealed several levels (Figs. 2, 3) of obstruction to the cephalad flow of contrast material. As in Case 1, the transient nature of the obstruction is evident, since the apparent obstruction is at higher levels in the later films.

CASE 3

Right brachial arteriogram. The catheter tip was advanced several inches into the vertebral artery. The first scout film, with hand injection of 2 ml of 50% Hypaque®, revealed dense filling of the entire vertebral artery. A second scout film, with hand injection of 8 ml of 50% Hypaque®, revealed a similar picture except that there now appeared to be a defect in the

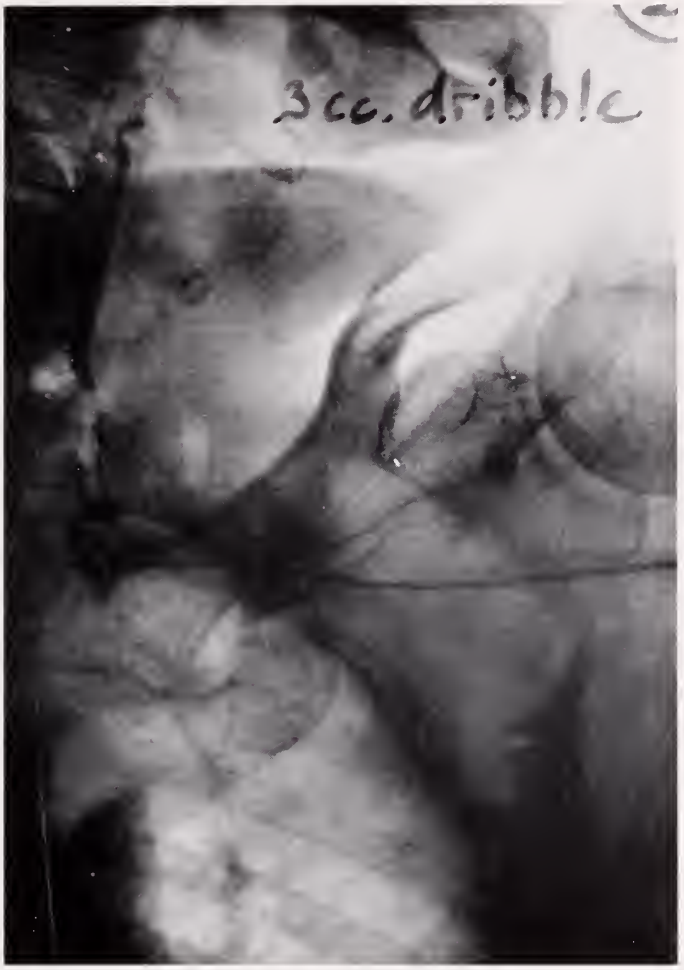

FIG. 3. Case 2. Subsequent injection demonstrates vertebral artery up to C3–4 region using only 2 ml contrast. Catheter in identical position to Fig. 2.

vertebral artery at the level of the C5-6 interspace. Serial intracranial arteriography was then attempted. No contrast material appeared in the posterior circulation but there was faint filling of the right carotid and its branches, suggesting that reflux had occurred. The catheter was withdrawn several inches until its tip lay in the subclavian artery somewhat distal to the vertebral orifice. A scout film revealed no vertebral artery filling except for a small stump near the origin (Fig. 4). Minutes later this patient had a left carotid arteriogram in which the left posterior cerebral artery was well visualized. It should be noted that a left carotid arteriogram performed four days previously had not demonstrated that artery.

Decreased flow through the posterior circulation secondary to spasm of one vertebral artery might account for this change. It has been shown that manual compression of the vertebral artery (2) during carotid arteriography can sometimes induce filling of the posterior communicating and posterior cerebral arteries. Figure 4 taken alone and out of context of the study might easily be interpreted as a proximal occlusion of the vertebral artery. The pre-

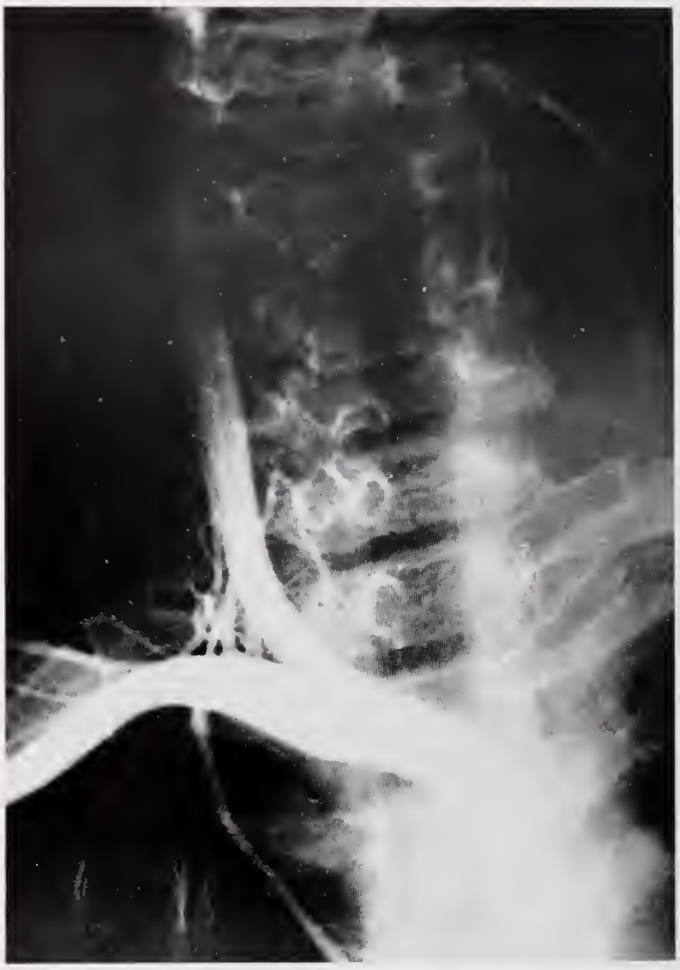

FIG. 4. Case 3. Catheter in right subclavian artery. Dense opacification of innominate, common carotid, subclavian, internal mammary and thyrocervical arteries. Only a small stump of vertebral fills out.

ceding films, however, indicate that the occlusion, whatever its nature, developed during the study. We believe this represents arterial spasm. The duration of this phenomenon is in some cases minutes; it is not yet clear how much longer it may persist.

2. Foramen Magnum Level

In this group the vertebral artery was densely filled with contrast material up to the region wherein the vertebral arteries unite to form the basilar artery.

(This region is designated the vertebro-basilar junction.) In these cases, there is a relatively sharp "cutoff" of contrast material at this point. A variant of this pattern consists of an incomplete block at the vertebro-basilar junction, with dense opacification up to the vertebro-basilar junction and very faint opacification past it. Retrograde filling of any portion of the contralateral vertebral has not been seen; this is in contrast to our experience with adequate normal vertebral arteriograms in which some portion of the contralateral vertebral artery is visualized in more than one-third of the cases. For this reason it is not always

FIG. 5. Case 4. Catheter in right vertebral artery. Normal vertebro-basilar arteriogram above, ten minutes following an identical procedure which had resulted in nonfilling of the posterior circulation and reflux right carotid filling.

possible to state with certainty whether the obstruction to cephalad flow occurs within the distalmost portion of the vertebral artery or actually within the basilar artery. In many of these cases, the ipsilateral posterior inferior cerebellar artery, including its branches, is well filled.

During a single study, prior or subsequent to the finding of an apparent occlusion, injection of contrast material demonstrated a normal vertebro-basilar arterial tree. In addition, the following findings, frequently noted in proved occlusions, were not present: a) retrograde filling of the upper basilar system during carotid arteriography; b) retrograde filling of superior cerebellar arteries from the distal posterior inferior cerebellar artery branches.

CASE 4

Right brachial arteriogram. The catheter tip was advanced several inches into the vertebral artery as demonstrated by one scout film using 2 ml of 50% Hypaque®. Serial arteriography revealed complete obstruction to the cephalad flow of contrast material in the vertebral artery at the level of the C2 vertebra. Simultaneously there was good filling of the right carotid artery and its branches, presumably by reflux. Papaverine® (32 mg (1 ml)) was then injected through the catheter. Subsequent serial studies indicated progressive changes. Two minutes later, a scout film revealed multiple defects along the vertebral artery with a sharp cutoff of contrast material proximal to the vertebro-basilar junction; ten minutes later, serial arteriography using 8 ml of 50% Hypaque® revealed excellent filling of the entire vertebro-basilar system including retrograde filling of the contralateral vertebral artery (Fig. 5). There

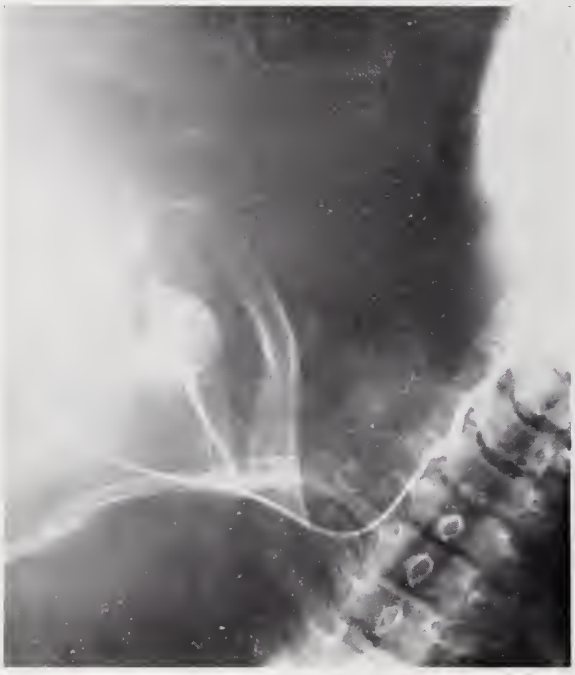

FIG. 6. Case 5. Catheter in right vertebral artery.

was residual contrast material in the right vertebral artery up to the vertebro-basilar junction throughout all nine films even though the left vertebral artery and the rest of the basilar system progressed normally through capillary and venous phases. From these observations, one may reason that the apparent occlusions were functional in nature since they were both variable in location and ultimately reversible.

CASE 5

Right brachial arteriogram. The catheter tip was advanced several inches into the vertebral artery (Fig. 6). A scout film revealed good filling of the vertebral (right) and basilar arteries. Serial arteriography with 8 ml of 50% Hypaque® revealed excellent filling of the entire vertebro-basilar system in the first arterial phase; in all subsequent films including late venous phases (Fig. 7), however, there was persistent dense opacification of the right vertebral artery up to the vertebro-basilar junction but no further intracranial filling. Papaverine® (3 mg) was then injected through the catheter. Ten minutes later, serial arteriography with 8 ml of

35% Hypaque® yielded an entirely normal study (Figs. 8, 9). The partial obstruction seen in the first set of films had disappeared.

CASE 6

Right brachial arteriogram. In this patient the apparent nature of the obstruction was verified by postmortem anatomic study. Hand injection was made with the catheter tip in

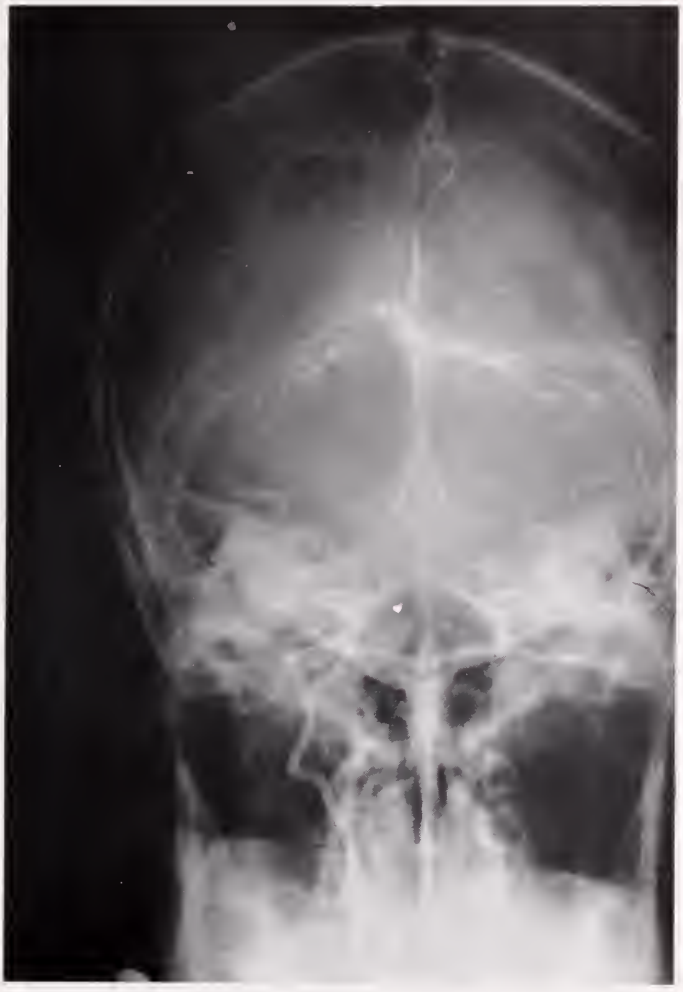

FIG. 7. Case 5. Entire right vertebral artery remains filled to foramen magnum level though intracranial filling has proceeded to late venous phase.

the right subclavian artery somewhat distal to the vertebral orifice. Serial arteriography with 20 ml of 50% Hypaque® revealed a densely filled right vertebral artery up to the vertebrobasilar junction. Beyond that point the basilar artery and its branches were not visualized but the posterior inferior cerebellar artery and its branches on the right were well filled (Fig. 10); there was persistent dense vertebral and posterior inferior cerebellar artery filling throughout all nine films. Twenty-seven days later the patient expired and a postmortem study was performed. The vertebral and basilar arteries were thin, translucent and their

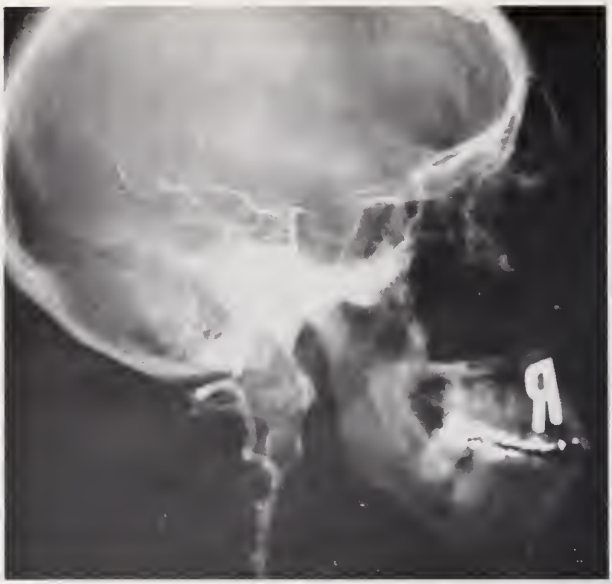

FIG. 8. Case 5. Ten minutes after Fig. 7, this repeat injection yielded normal filling.

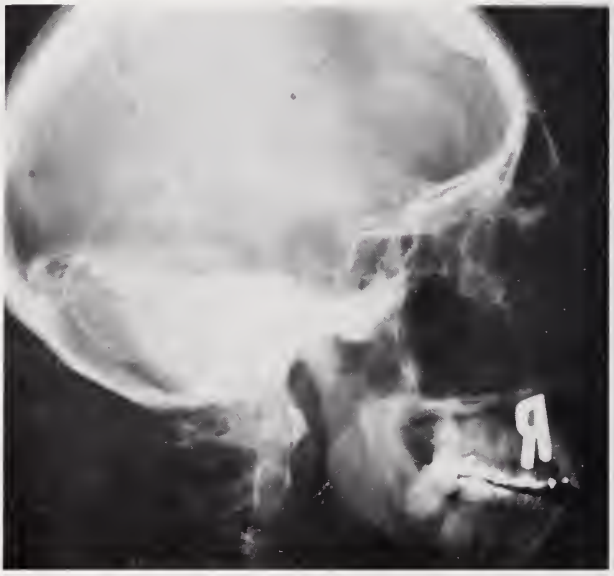

FIG. 9. Case 5. Same series as Fig. 8, venous phase; in this series the cervical vertebral artery no longer remains filled throughout the study as in Fig. 7.

lumens widely patent throughout. There was no obstruction and no segmental atresia of the right vertebrobasilar junction.

DISCUSSION

The studies of Roy and Sherrington suggested that in physiological preparations the cerebral vasculature does not undergo spasm since it does not possess

an autonomic nerve supply (3). It should be apparent that this does not preclude the occurrence of spasm; rather, it may involve mechanisms different from the sympathetic control which occurs elsewhere in the body. Spasm of the intracranial vasculature does, in fact, occur (4–12), as has been demonstrated in the region of ruptured aneurysms (13–16).

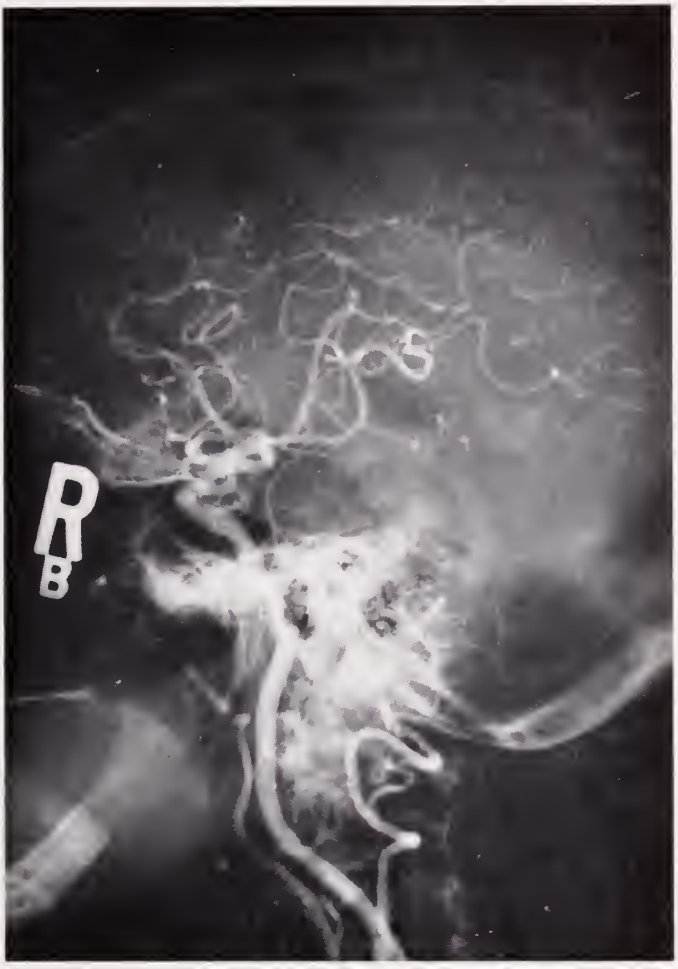

FIG. 10. Case 6. Catheter in right subclavian artery. No contrast passed beyond foramen magnum region in the vertebro-basilar system. Vertebral artery remained filled as above throughout this serial arteriogram.

Since the vascular occlusions encountered here were reversible in some way in each of the five arteriographically proved studies and absent in the patient with a postmortem examination, we have considered this pattern of occlusion to represent spasm. It should be apparent that the ultimate proof of the nature of these apparent occlusions must depend upon arteriographic reversibility or postmortem evidence. It should be emphasized that the diagnosis of, and differentiation among, spasm, occlusion and atresia must not be based upon inade-

quate criteria such as the radiographic appearance of the actual site of an occlusion.

Our data seem to indicate that intramuscular Papaverine® in the dosage employed has no significant effect upon the frequency with which spasm is encountered (17). The number of studies in which Papaverine® was administered intra-arterially once spasm had occurred is still too small to warrant any conclusion.

In this series all arteriograms were performed with the head directed straight forward, since general experience suggests that vertebral filling may be affected by lateral rotation of the head.

SUMMARY

1. In a series of 86 vertebral arteriograms performed by brachial catheterization a pattern suggestive of vertebral occlusion but best explained as arterial spasm was encountered.

2. Criteria for the radiographic diagnosis are presented and illustrated.

3. Pitfalls in differentiating occlusion and atresia from spasm are stressed.

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Clinical Evaluation of Pargyline Hydrochloride, (A New Monoamine Oxidase Inhibitor), in Primary Hypertension

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Interest in the role of monoamine oxidase (MAO) inhibitors in the treatment of hypertensive disease has been stimulated recently, by the introduction of a new drug, pargyline hydrochloride, with powerful MAO inhibiting properties. This new chemical structure does not have the hydrazine configuration which is thought to predispose to the liver toxicity (1–4), visual disturbances (3–5) and optic atrophy (3, 6) that have been reported as side effects of MAO inhibitor administration. It is, nevertheless, a powerful and irreversible inhibitor of MAO *in vivo* and *in vitro* with a potency 7 to 10 fold that of iproniazid. These considerations prompted our investigation of the antihypertensive effect of pargyline hydrochloride in patients with primary hypertension since there is evidence that adequate antihypertensive drug treatment of patients with primary benign hypertension significantly prolongs survival, reduces the incidence of complications and affects the signs and symptoms of the disease favorably (7–20).

METHODS

Twenty-seven ambulatory patients from the Hypertension Outpatient Clinic of The Mount Sinai Hospital were selected at random and studied. All the subjects had documented untreated primary benign hypertension for at least nine months prior to their inclusion in this study. Each patient was examined at intervals of two weeks and after two biweekly control periods elapsed in which the subjects were given placebo medication, the pargyline hydrochloride (N-benzyl-N-methyl-2-propynylamine hydrochloride) was prescribed. Dosage was adjusted at each clinic visit until the optimum antihypertensive effect was achieved or side effects appeared. The average therapeutic dose of pargyline hydrochloride in these 27 patients was 50 mg.

The classification of the primary benign hypertensive patients into three groups designated "mild," "moderate" and "severe" has been previously described (20). Briefly, the severe group was composed of patients with systolic and diastolic blood pressures above 190 mmHg and 120 mmHg, respectively, with involvement of two or more organs by the hypertensive disease. The mild group consisted of patients with blood pressures above 150 mmHg systolic and 100 mmHg diastolic without evidence of organ involvement attributable to hypertensive disease. The moderate group was composed of patients with intermediate criteria.

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The antihypertensive response to pargyline hydrochloride therapy was classified as "good," "fair" and "poor." A blood pressure decline to normal or near normal values together with regression of organ involvement when present was designated a good response. A poor response was little or no blood pressure decline unassociated with regression of organ involvement when present. A fair response was intermediate between good and poor.

TABLE I

Results of Treatment with Pargyline Hydrochloride in 27 Subjects with Primary Hypertension

Severity of Hypertension	Treatment Results			Total Number of Patients
	Good	Fair	Poor	
	No. of Patients			
Mild	7	1	2	10
Moderate	2	1	1	4
Severe	7	4	2	13
Total	16	6	5	27

TABLE II

Results of Treatment in 152 Subjects with Primary Hypertension

Severity of Hypertension	Treatment Results			Total Number of Patients
	Good	Fair	Poor	
	No. of Patients			
Mild	15	4	1	20
Moderate	23	12	12	47
Severe	30	25	30	85
Total	68	41	43	152

RESULTS

A summary of the results of treatment with pargyline hydrochloride in 27 primary benign hypertensive subjects is recorded in Table I. A good result was demonstrable in 16 of the 27 patients and a good or fair result was obtained in 22 subjects. It is interesting to note that the incidence of good results was almost as great in the severe group of patients with primary hypertension as in the mild group. This observation contrasts with results obtained recently in an unselected group of 152 patients with primary hypertension treated with a wide variety of antihypertensive preparations, either singly or in combination. The results of this study have been reported previously (20) and are reproduced in Table II. The results of treatment with a variety of antihypertensive preparations in the 152 subjects with primary hypertension were not as favorable as the

results obtained with pargyline hydrochloride. Only 45 per cent of the 152 subjects demonstrated a good result and 72 per cent had a good or fair result.

A variety of side effects was recorded in the 27 subjects treated with pargyline hydrochloride. Nausea was the most frequent side effect. It was recorded in four patients who obtained a good result, one patient with a fair result and three patients with a poor result. Troublesome postural hypotension with dizziness, usually on assuming the erect position, was seen in six patients. Weakness, diarrhea and a peculiar oral taste were each recorded in two subjects. There was no alteration of hepatic or hematological function during the course of this nine month study.

DISCUSSION

This clinical investigation emphasizes the beneficial results that may be obtained in subjects with primary hypertension when treated with an antihypertensive drug. The incidence of good results in the present communication is greater than the 45 per cent good results obtained in the series of 152 subjects with primary hypertension treated with a variety of antihypertensive preparations reported previously (20) and the 42 per cent good results obtained in a similar series reported earlier (13). Although each of these three series were comparable in patient selection, the relatively small number of subjects in the present series suggests that the favorable results be interpreted in this context. Favorable results in the treatment of primary hypertension with pargyline hydrochloride have also been recorded by other investigators (21, 22).

The mechanism of action of MAO inhibitors has been studied carefully with variable conclusions. Diminished responsiveness of the peripheral vascular system to norepinephrine due to an increased norepinephrine content of the blood vessels has been suggested (23–25). Blockade of norepinephrine release at neuroeffector junctions by MAO inhibitors (26, 27) has also been proposed but is probably a contributing factor at best. Adrenergic blockade (23) and depression of central sympathetic centers (23) are also unlikely. The best experimental evidence suggests that MAO inhibitor administration lowers the blood pressure by blockade of sympathetic ganglia (23, 28–32).

It is apparent, therefore, that MAO inhibitors offer a new approach to the treatment of hypertension in man because of their freedom from parasympathetic side effects and pronounced psychic stimulant and anti-anginal properties. The results of this study support the use of pargyline hydrochloride as an effective MAO inhibitor and antihypertensive agent in man.

ACKNOWLEDGMENT

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The Drug Treatment of Primary Hypertension with Alpha Methyl Dopa Combined with Hydrochlorothiazide

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The successful use of rauwolfia alkaloids, bretyllium tosylate, guanethidine and certain monoamine oxidase inhibitors in the treatment of hypertension, has made it quite apparent that interference with the biosynthesis, metabolism and release of catecholamines is an effective method of controlling elevated blood pressure. The demonstration that dopa decarboxylase inhibition interferes with catecholamine synthesis (1–2) and that 3,4-dihydroxy-d-1-phenylalanine (alpha methyl dopa), a decarboxylase inhibitor, had potential antihypertensive action (3, 4), led to its introduction into the antihypertensive therapeutic armamentarium. Recent clinical trials of this drug in the treatment of hypertension have shown that it has sedative and hypotensive properties (5–8). Alpha methyl dopa is effective in all grades of hypertension, reducing recumbent as well as standing blood pressure. Side effects have thus far been limited to early drowsiness, and orthostatic hypotension. There have been two reported cases of transient fever, of which one was associated with reversible liver function abnormalities (5).

The pharmacodynamic effect of this drug is limited to the L-isomer (9) and seems unrelated to decarboxylase inhibition (4, 10). The exact mechanism of action of alpha methyl dopa is not clear but may involve sympathetic blockade at a central or peripheral site (10). It was recently suggested that alpha methyl dopa depletes tissue catecholamine stores. This action has been ascribed to decarboxylation of the drug and possibly of norepinephrine to produce amine metabolites, which have been shown to cause depletion of tissue catecholamines in the brain, sympathetic nerves and chromaffin tissue (11). The effect of alpha methyl dopa on the digital circulation of hypertensive patients would indicate that it reduces peripheral arterial resistance (12).

The potentiating effect of chlorothiazide and its congeners in antihypertensive regimens is well known and has been documented with alpha methyl dopa (13). The purpose of this study was the evaluation of alpha methyl dopa when combined with hydrochlorothiazide in various dosage regimens.

MATERIAL AND METHODS

The study was designed and conducted on a double blind basis and alpha methyl dopa with hydrochlorothiazide was supplied in identical capsular form

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in the following combinations:

alpha methyl dopa: 125 mg and hydrochlorothiazide: 25 mg
alpha methyl dopa: 250 mg and hydrochlorothiazide: 25 mg
alpha methyl dopa: 250 mg and hydrochlorothiazide: 15 mg

The capsules were packaged in 12 separate bottles each containing a two week supply of the medication. The 12 bottles containing the medication for each patient bore only the patient number and the period number, the latter representing the 12 consecutive two week treatment periods. Each of the above three combinations were given for four consecutive two week periods. A sealed envelope containing a code identifying which combination the patient was receiving at a particular time of the study was sealed at the time the medication was packaged and numbered. The envelope remained sealed throughout the duration of the study.

Nineteen patients were selected for the study from the Hypertension Clinic. The patients had established essential hypertension and had been treated previously with various other antihypertensive regimens. Patients with severe degrees of renal involvement and with malignant or accelerated hypertension were excluded from the study. The patients were admitted to the study after a two week control period during which time no medication was given and control blood pressure readings were recorded in the standing and recumbent positions. Patients were seen at two week intervals thereafter. Blood pressure readings were recorded in the same manner and the subjects were carefully questioned regarding symptoms and possible side effects. Hemoglobin levels, white blood counts, serum glutamic oxaloacetic transaminase, albumin and globulin, bromsulphalein disappearance, urinalysis and blood urea nitrogen determinations were obtained in all patients during the control period, before medication was given, at the end of the fourth two week period and again at the completion of the study. Patients were seen again two weeks after completion of the study, during which time no medication was given.

RESULTS

Of the nineteen patients originally selected for this study, 13 patients completed the 14 two-week periods of therapy. Of the six remaining patients, five were lost to follow-up in the early stages of the study and one patient suffered a myocardial infarction during the 6th period.

The medication, given thrice daily during the study, contained the following combinations:

Medication A: alpha methyl dopa: 125 mg and hydrochlorothiazide: 25 mg
Medication B: alpha methyl dopa: 250 mg and hydrochlorothiazide: 25 mg
Medication C: alpha methyl dopa: 250 mg and hydrochlorothiazide: 15 mg

Each combination was administered for four consecutive two-week periods.

The results tabulated in Table I represent the mean recumbent and standing blood pressure readings obtained during the control period and during therapy with medications A, B and C. Also included is a statistical analysis comparing the mean recumbent and standing blood pressure readings during the control

period to blood pressure readings during the administration of medications A, B and C respectively.

Mean control blood pressures were 189/118 recumbent and 178/115 standing. Mean blood pressure readings during medications A, B and C were not significantly different from each other in the standing or recumbent position and were as follows:

Medication A: 156/102 recumbent and 144/95 standing;
Medication B: 153/101 recumbent and 138/92 standing;
Medication C: 151/91 recumbent and 139/92 standing.

Comparison of the mean control recumbent and standing blood pressures with blood pressures during medications A, B and C respectively revealed a statistically significant difference in each comparison. ($P < 0.01$ in each). Mean standing and mean reclining blood pressure readings obtained during treatment with medications A, B and C were not significantly different from each other. Al-

TABLE I

	Control		Medication A		Medication B		Medication C	
	Rec.	Stand.	Rec.	Stand.	Rec.	Stand.	Rec.	Stand.
Mean B.P. $\frac{\text{Systolic}}{\text{Diastolic}} = \bar{X}$	189	178	156	144	153	138	151	139
	118	115	102	95	101	92	97	92
* Pooled variance = S^2			664	663	708	815	882	836
			184	208	210	221	221	204
* P value			<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

* Comparison of Mean Control B.P. Readings with Groups A, B and C respectively.

though standing blood pressure readings were uniformly lower than recumbent blood pressure readings, the differences were not statistically significant in the control period nor during the three medication periods.

Side effects encountered with the three combinations of alpha methyl dopa and hydrochlorothiazide were minimal. The hypotensive effects, more marked in the standing position, led to occasional, transient morning dizziness in seven patients. Drowsiness during the first two to three days of treatment occurred in 17 of the 19 patients and persisted, to a mild degree, in 5 patients throughout the study. Two patients complained of transient morning weakness during the study and four patients experienced nausea and anorexia which were more marked during the early stages of the study. The severity of the side effects did not necessitate discontinuation of the study in any of the subjects. There was no definite correlation between the occurrence or severity of the side effects and the type of combination used. The one patient in whom myocardial infarction occurred had had effort angina for three years. Although he had severe hypertension, the mean blood pressure readings prior to myocardial infarction and during the study were 160/110 recumbent and 160/105 standing as compared to a control of 230/120 recumbent and standing. The hemograms, urinalyses and

liver function tests obtained before, during and after the study did not reveal any abnormalities.

DISCUSSION

The results confirm the reported hypotensive properties of alpha methyl dopa and indicate that this drug can safely be combined with hydrochlorothiazide in the treatment of hypertension. It was, however, not possible to separate the antihypertensive effect of the one drug from the other in this study. Significant lowering of the blood pressure levels occurred in all patients but there was no significant difference in the hypotensive action of the three different combinations used. Medication A, containing alpha methyl dopa 125 mg and hydrochlorothiazide 25 mg, which was administered thrice daily was as effective in reducing the blood pressure in these 13 patients as combination B and C, containing alpha methyl dopa 250 mg and hydrochlorothiazide 25 mg and 15 mg respectively. It would therefore appear from this study that combination A is the most economical one and as effective as the others.

The results obtained in this study using three different fixed combinations of two drugs were generally good. However, since the individual requirements of alpha methyl dopa can vary, it is probably preferable to administer the two drugs separately and according to the requirements of each patient.

The side effects encountered in this study were mild. Although the hypotensive effect was greater in the standing position, recumbent blood pressures were also appreciably reduced. The only clinical manifestation of the orthostatic effect was occasional transient dizziness in seven patients. Severe orthostatic hypotension with fainting did not occur in any of the patients studied. The occurrence of myocardial infarction in one patient was disturbing. It is, however, doubtful that its occurrence was related to use of the drug.

SUMMARY AND CONCLUSIONS

In a double blind study, three combinations of alpha methyl dopa and hydrochlorothiazide were administered to 13 patients for a total period of 24 weeks, in an effort to find the best combination. All medications were given three times daily.

Medication A, containing alpha methyl dopa 125 mg and hydrochlorothiazide 25 mg, was as effective a hypotensive agent as the other two combinations containing alpha methyl dopa 250 mg and hydrochlorothiazide 25 and 15 mg respectively.

The hypotensive action of alpha methyl dopa in the recumbent and standing position and its potentiation by hydrochlorothiazide were confirmed in this study. The use of fixed combinations, however, is probably less desirable than separate dosage regulation.

Side effects were minimal consisting of transient early morning dizziness in seven patients. Anorexia and nausea occurred in two patients. Severe orthostatic hypotension did not occur. Myocardial infarction occurring in one patient was not believed to be related to use of the drug.

ACKNOWLEDGMENT

We are grateful to Dr. E. L. Foltz of the Merck, Sharp and Dohme Pharmaceutical Company, West Point, Pennsylvania, for the generous supplies of "Aldomet" used in these studies. The secretarial help of Mrs. Rita Mileznski is gratefully acknowledged.

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Lupus Vulgaris-like Reaction Following BCG Vaccination

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Lupus vulgaris following BCG inoculation is a rare occurrence. No such case could be found in the American literature. The purpose of this paper is to report a lupus vulgaris-like reaction at the site of a BCG vaccination and briefly to review the literature on this subject.

CASE REPORT

A three month old male child of Puerto Rican lineage, was admitted to The Mount Sinai Hospital in July 1961 because of a rash over the right deltoid area. This was the site of BCG inoculation given at the age of three days using a multiple puncture grid. The baby's mother had been treated for tuberculous cervical lymphadenitis three years previously but had no active tuberculosis at the time of vaccination of her child. The pregnancy was normal and uncomplicated. Birth and delivery were also normal and the birth weight was 7 lb 10 oz.

Within a week after inoculation, the infant had redness over the right deltoid region. Treatment with penicillin and topical ointments was followed by improvement. Twenty weeks later the patient was seen in the Emergency Room. He had a temperature of 101° rectally and there was a papular, erythematous, eruption over the right deltoid area (Fig. 1). The papules were indurated and there was a small draining sinus. The parents noted tenderness in the area. There were tender submaxillary and right axillary nodes.

Second strength intradermal PPD was positive. The hemoglobin was 12.5 Gm. White blood count was 6,850, 58 segmented PMN's, 2 bands, 38 lymphocytes, 2 eosinophiles, 1 monocyte. Urine specific gravity 1.016, acid, trace albumin, 1–2 red blood cells, 4–5 white blood cells. The chest X-ray was normal. Cultures of gastric aspirates were negative for acid fast bacilli. A skin biopsy confirmed the clinical impression of lupus vulgaris: "within the dermis and reaching in places to the dermal-epidermal junction, there is an infiltrate of mononuclear cells, some of which have the typical appearance of epithelioid cells. The majority, however, are lymphocytes and scattered small histiocytes. An occasional typical Langhans giant cell is observed. Here and there, the epithelioid cells formed distinct tubercles. The dermis away from the infiltration is somewhat edematous and shows an increase of fibroblasts and dilated vessels. The epidermis overlying the most massive infiltrate shows acanthosis and a thick parakeratotic scale" (Fig. 2). Stain of biopsy material for acid fast bacilli was negative.

The infant was started on a regimen of INH 60 mg daily and para-amino-

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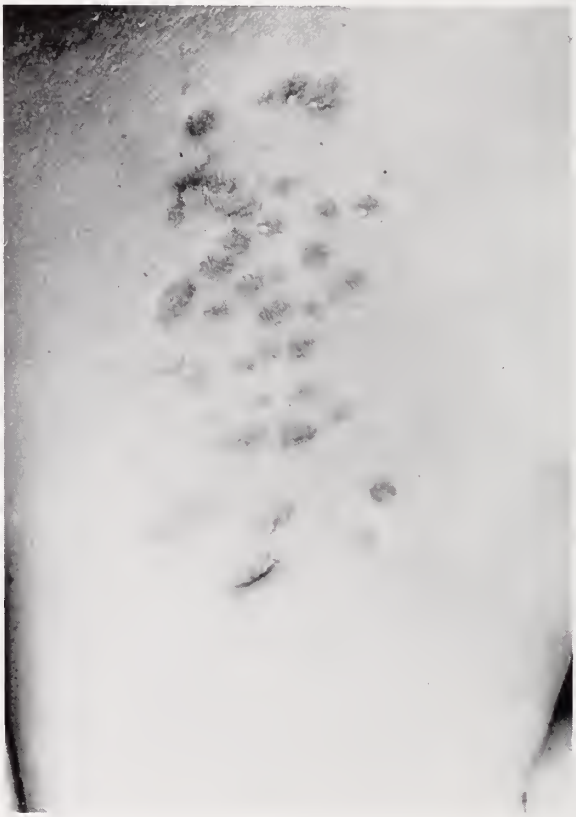
This case was presented at the Dec. 6, 1961 meeting at the New York Academy of Medicine Section of Dermatology.

salicylic acid 1.5 Gm daily and was followed in both Pediatric and Skin clinics. The erythematous papules persisted until five months after he was seen in the Emergency Room with the eruption. At this time he was seen at the Skin Clinic and there was no significant adenopathy. Growth and development were normal. At the age of six months he weighed 13 lbs 3 oz. One year following hospitalization the child was seen again. He was alert and happy. The only remnant of BCG inoculation over the right arm was a faded, sightly pitted scar measuring

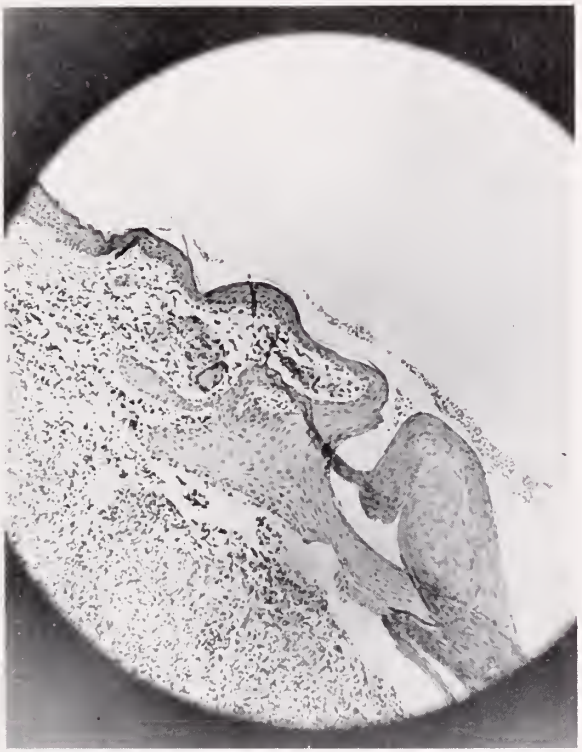


5.0 cm by 1.6 cm (Fig. 3). There was no significant adenopathy. Weight was 22 lbs 14½ oz. Height was 80 cm. Chest X-ray was normal and there were no soft tissue calcifications seen in the neck. There was no evidence of generalization. Second strength PPD was positive. The hemoglobin was 9.0 Gm%. White count was 9,000, 40 PMN's, 8 bands, 38 lymphocytes, 9 monocytes, 8 eosinophiles. It was thought that the child had mild iron deficiency anemia and he was started on daily iron therapy. INH and PAS were discontinued after nine months of therapy.

The BCG batch was checked and there were no other reports of any untoward reactions. The child was vaccinated in the newborn nursery at Mount Sinai

Hospital on April 20, 1961. To date, no case has been reported from the United States of lupus vulgaris or of a lupus vulgaris-like reaction following BCG vaccination.

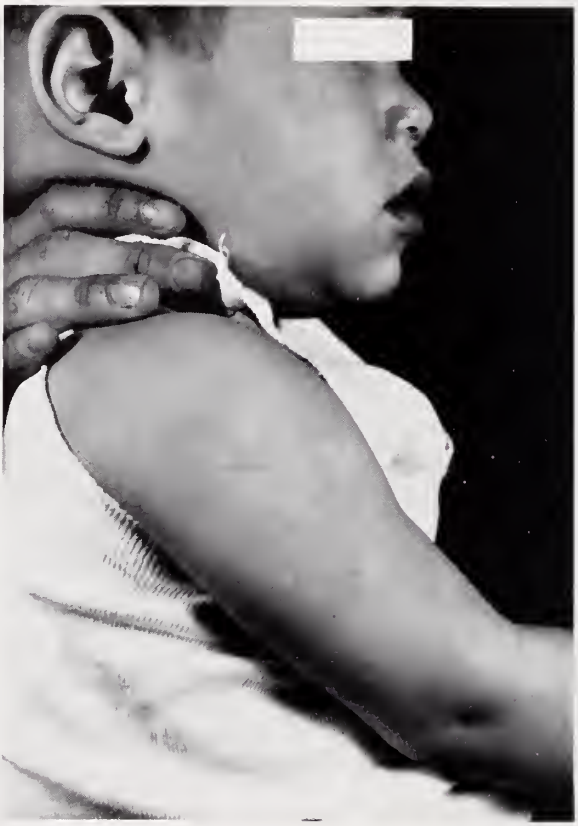
In a review of the world literature, a total of forty similar cases outside the United States were found to 1959 (1, 2). Of these, four occurred in infants. Since 1959, we have been unable to find any reports of a post-BCG lupus vulgaris-like reaction in infancy. However, Vissian (3), and others (4, 5), have reported cases



in adults. These bring the total number of cases to 45. We believe ours is the 46th. It is also noteworthy that it is the fifth case occurring in infancy.

The usual result of BCG vaccination is a chancre of low virulence which heals (6). Disappearance of the cutaneous reaction except for a pale scar occurs in the guinea pig by the eighth week (10). In their experimental studies, Vogelsang and Wetteland found no trace left on the skin of any animal in the eighth week after inoculation. Generally, the clinical course of the primary skin response to BCG vaccination by intracutaneous injection in the guinea pig imitates fairly well the response to the same procedure in the uninfected human being (11). Untoward reactions to inoculation are uncommon. Of 18,409 Ghana children vaccinated with BCG only twenty untoward reactions were noted by Koch in 1961, a morbidity of 0.1 per cent. The rarity of this occurrence is further illus-

trated by the report of Gemmill (8). Of approximately 40,000 children vaccinated with BCG there were 329 complications, predominantly infections, with only one lupus vulgaris. In a fatal reaction to BCG vaccination, autopsy revealed lesions at the site of inoculation as well as in the lymph nodes, lungs, and spleen. Experimentally, it has been shown in the guinea pig that one week after inoculation with BCG, viable organisms could be cultivated from the lymph nodes, and spleen. Sometimes, organisms could be isolated from lungs and tracheobroncheal



lymph nodes. However, in the case reported by Ariztia, "there was in these organs an inflammatory reaction with exudate of lymphocytes, histiocytes, and epithelioid cells resembling those found in tuberculous lesions without the characteristic tubercles or caseation." Why the reaction occurred is not known. The author offers two possible explanations: 1) Increased virulence of the bacillus used, 2) A special individual condition creating appropriate ground for dissemination.

In the case here reported an explanation for the lupus vulgaris-like reaction might be either increased virulence of the bacillus used, possibly too deep penetration of the vaccinating material, possibly increased size of the inoculating

dosage, or a change in the allergic state of the infant making him more susceptible.

In few of the previous reports is mention made of treatment of the lupus vulgaris. Of data available on 10 treated cases, 3 were treated with INH and PAS and made good recovery. Boulle's case was treated with INH 150 mg daily for two months and made a complete recovery within a year. These reports regarding treatment are in agreement with our experience in which the patient was given both INH and PAS. Other reported treatments which produced good results were combinations of INH, streptomycin and calciferol, and streptomycin alone. One case was treated with complete excision followed by improvement.

SUMMARY

A case of lupus vulgaris-like reaction following BCG inoculation in a newborn is reported. This was treated with INH and PAS with complete disappearance of lesions several months after the institution of therapy. After one year the child is well. We have reviewed the possible explanations for the development of this unusual complication and have reviewed the pertinent literature.

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RADIOLOGICAL NOTES

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The following six cases are presented as a group because each posed the diagnostic problem of a large intra-abdominal mass. They were selected because they demonstrated similar unusual and often atypical features from a roentgen standpoint. They will be discussed together following the case presentations.

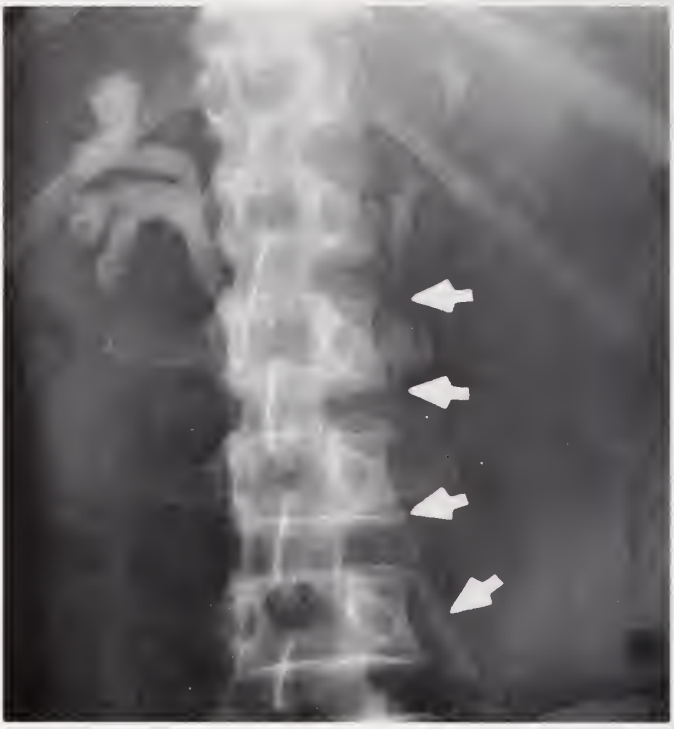

FIG. 1. Intravenous pyelogram reveals that the homogeneous mass displaces the left ureter in its middle two-thirds both medially and posteriorly (along arrows). The collecting systems are otherwise normal.

CASE NO. 198

A 52 year old male was admitted to the hospital with a one year history of increasing abdominal swelling associated with slight anorexia, fatigue and weight loss. During the previous three months, the patient also noted edema of both lower extremities. There was one episode of melena. Physical examination revealed an emaciated patient with a very protuberant abdomen. No discrete masses or organ enlargement were delineated. An abdominal fluid wave could be elicited. Laboratory examination revealed a microcytic anemia with a hemo-

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globin of 9.5 Gm% and a slightly elevated erythrocyte sedimentation rate. X-ray examination of the abdomen revealed a generalized hazy density without definite borders occupying the upper two-thirds of the abdominal cavity. The air-containing stomach appeared to be pushed upwards and the small bowel was displaced to the right by this mass. The gas-filled splenic flexure demonstrated a lobulated indentation upon the medial aspect of the proximal descending colon. Intravenous pyelogram revealed the collecting system of both kidneys to be intrinsically normal. There was considerable displacement of the left

Fig. 2. Gastrointestinal series reveals an irregular contour defect upon the middle third of the greater curvature of the stomach (arrows). In the center, there is dimpling of the mucosa with indistinctness of the folds. This may represent a small area of ulceration.

ureter by this mass, both posteriorly and medially (Fig. 1). There was no evidence of hydronephrosis. Barium meal revealed an irregular contour defect of the middle third of the greater curvature of the stomach. On some of the films, there was a constant dimpling in the mid-portion of this pressure defect with indistinct rugal folds suggesting the possibility of a small ulceration (Fig. 2). The ligament of Treitz was noted to be displaced by this large mass both medially and downwards. Small bowel examination revealed displacement of the small bowel loops to the right of the abdomen. In the lateral projection, both the small and large bowels were noted to be displaced posteriorly as well (Fig. 3). The soft tissue mass was seen to be situated anteriorly and its posterior

margin was sharply delineated inferiorly. Barium enema examination revealed the colon to be intrinsically normal. The transverse colon was noted to be displaced upwards and posteriorly and the descending colon also was displaced backwards by the mass (Fig. 4). Diagnostic paracentesis was then performed and 9,000 cc of hemorrhagic fluid were removed. This fluid contained many

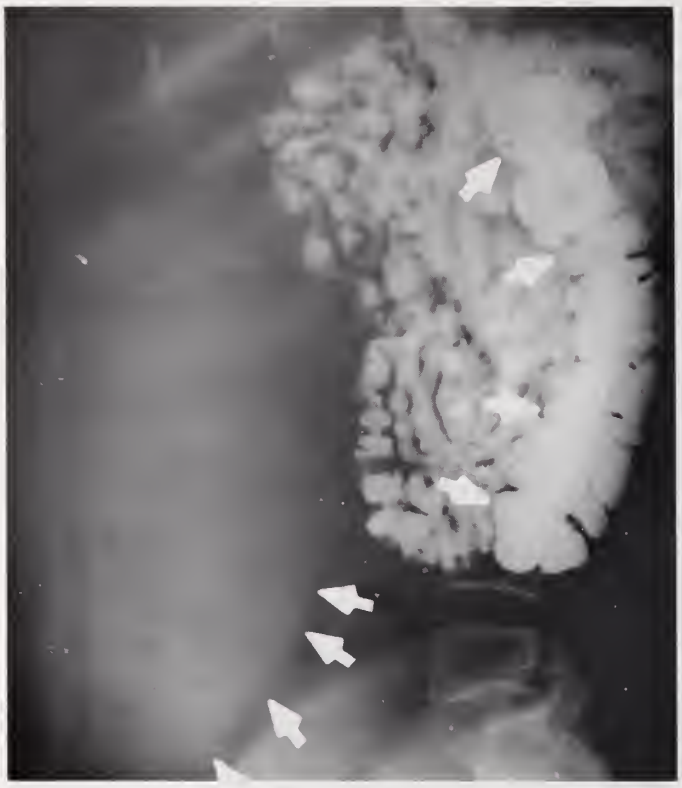

FIG. 3. Lateral view of the abdomen in the course of a small bowel examination reveals that the mass is situated anteriorly and is well demarcated inferiorly and posteriorly (lower arrows). The small intestine and colon are displaced posteriorly (upper arrows).

lymphocytes. Cytologic examination revealed the presence of numerous cells suspicious of malignancy. Laparotomy was then performed and a large degenerating tumor was found occupying most of the upper abdomen. It was noted to be attached by a narrow base to the greater curvature of the stomach. The cystic mass measured 30 × 20 × 20 cm in size and was removed together with a small cuff of stomach. Histologic and pathological study revealed a huge partially necrotic leiomyosarcoma.

Case Report: EXOGASTRIC LEIOMYOSARCOMA.

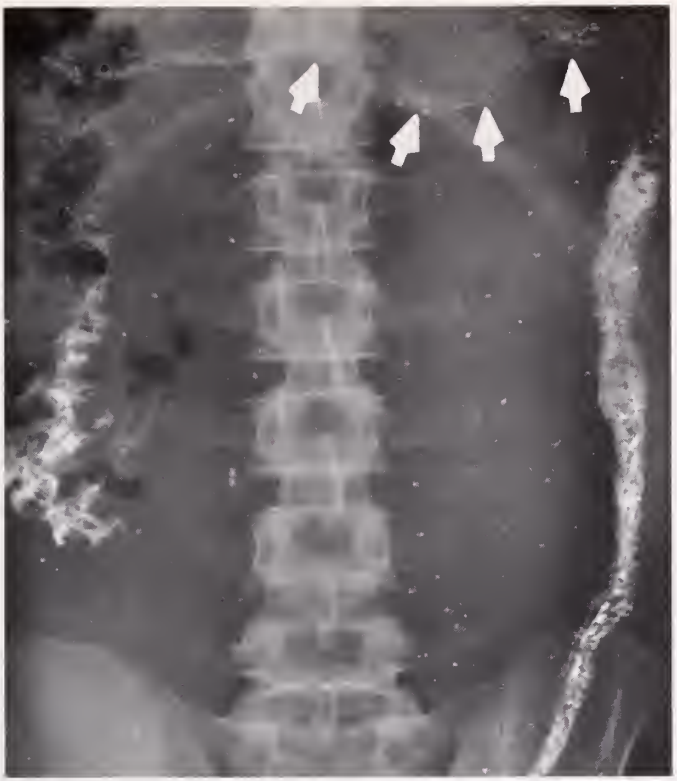

FIG. 4. Barium enema reveals that the transverse colon is displaced upwards by the large abdominal mass (arrows).

CASE NO. 199

A 74 year old male was admitted to the hospital with a three-month history of increasing abdominal swelling. The patient also noted dull lower abdominal pains of increasing severity together with progressively severe constipation. A few days before admission, he noted several episodes of bright red blood in his stools. On examination, a 20 × 10 cm mobile and nodular mass was palpated in the lower abdomen. A smooth liver edge extended three fingersbreadth below the costal margin. The patient had a microcytic anemia of 10 Gm% and guaiac positive stools. Intravenous pyelogram revealed a large mass occupying the lower half of the abdomen. The urinary tract appeared intrinsically normal. There was no evidence of displacement of the kidneys or ureters. Barium meal examination disclosed a normal stomach and duodenum. The jejunal loops were displaced upwards and laterally by the large lobulated mass. There was a long segment of ileum which appeared to be intimately adherent to the mass over most of its extent (Fig. 1). On the left side of the abdomen, there was a rather acute constant angulation at the proximal end of this segment with marked irregularity of the mucosal pattern immediately distal to the bend. Details of

the mucosal pattern were difficult to delineate because of marked narrowing of the lumen and irregular filling. This was interpreted as probably representing the point of attachment of the tumor to the small bowel. Barium enema examination revealed no abnormality.

At operation, a large melon-sized, lobulated tumor was noted in the lower loops of jejunum. It was attached to the small bowel and to the mesentery.

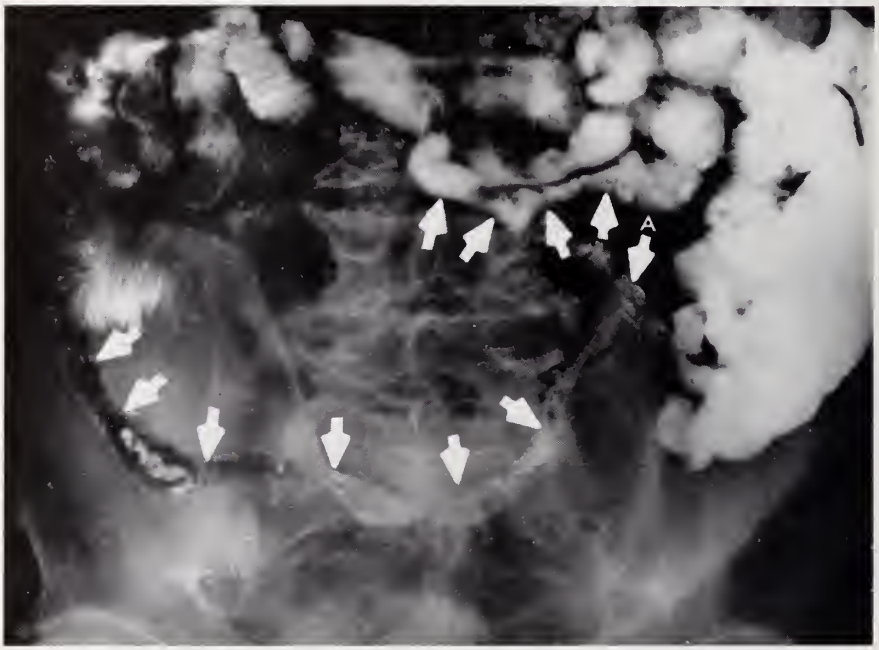

FIG. 1. Small bowel series reveals a large lobulated mass displacing adjacent loops of jejunum and ileum (upper arrows). There is one long segment of ileum that appears to be intimately adherent to the mass over much of its diameter (lower arrows). On the left side of the abdomen, at the proximal end of this loop, there is an acute angulation of the bowel loop (arrow A). The mucosal pattern just distal to this angulation is indistinct with some irregularity. Details of the mucosal pattern are difficult to delineate because of marked narrowing of the lumen and irregular filling. This is interpreted as probably representing the point of attachment of the tumor to the bowel.

Multiple metastatic deposits were seen within the right lobe of the liver. The entire tumor was removed and an end-to-end anastomosis was performed. The patient made an uneventful recovery.

Case Report: SMALL BOWEL LEIOMYOSARCOMA.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Selig M. Ginsburg and Dr. Daniel Luger.

CASE NO. 200

A seventy-five year old male was admitted to the hospital because of an enlarging right upper quadrant mass of two months' duration. Seven months prior to admission, the patient was hospitalized at another institution for melena. At this time a barium meal examination was reported as normal. However, one

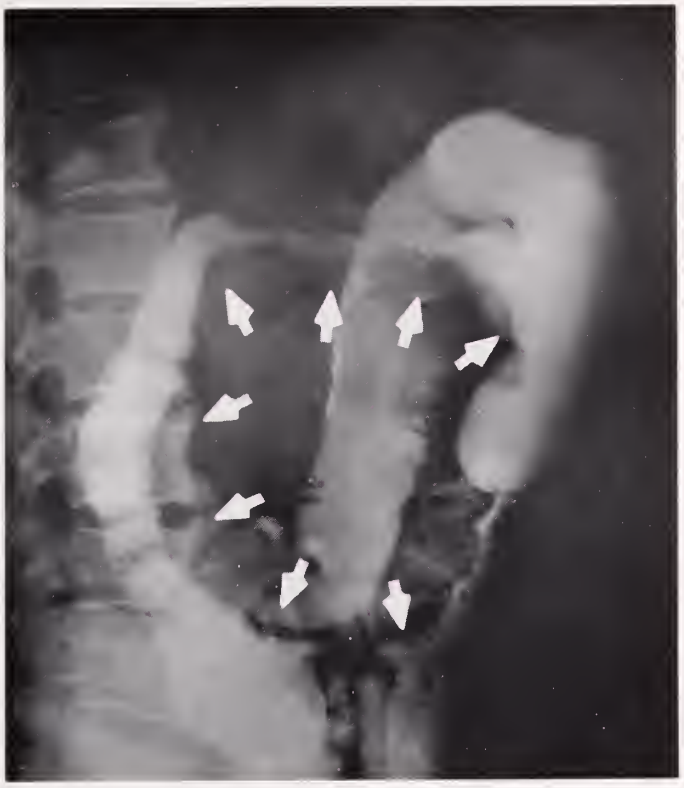

Fig. 1. Lateral view of the abdomen during barium enema demonstrates extrinsic pressure and displacement of the colon and terminal ileum. The hepatic flexure and proximal transverse colon are draped over a mass (upper arrows). The ascending colon and terminal ileal loops are also displaced (lower arrows).

month prior to admission, repeat barium enema examination revealed a narrowing in the proximal transverse colon. The patient had anorexia and had lost weight progressively over the past six months. The patient was a known mild diabetic.

Physical examination revealed a large, hard, smoothly outlined mass occupying the right upper quadrant from which the liver outline could not be distinguished. Routine examinations of the blood and urine were normal. Barium enema examination revealed marked displacement of the hepatic flexure and proximal transverse colon by a mass measuring approximately 15 x 12 cm (Figs.

1, 2). The ascending colon and terminal ileal loops were also displaced by the mass. The bowel was not involved intrinsically, but appeared to be fixed and stretched by the mass. Nephrotomogram demonstrated the integrity of the right renal outline, but the kidney was displaced upwards (Fig. 3). A rich supply of

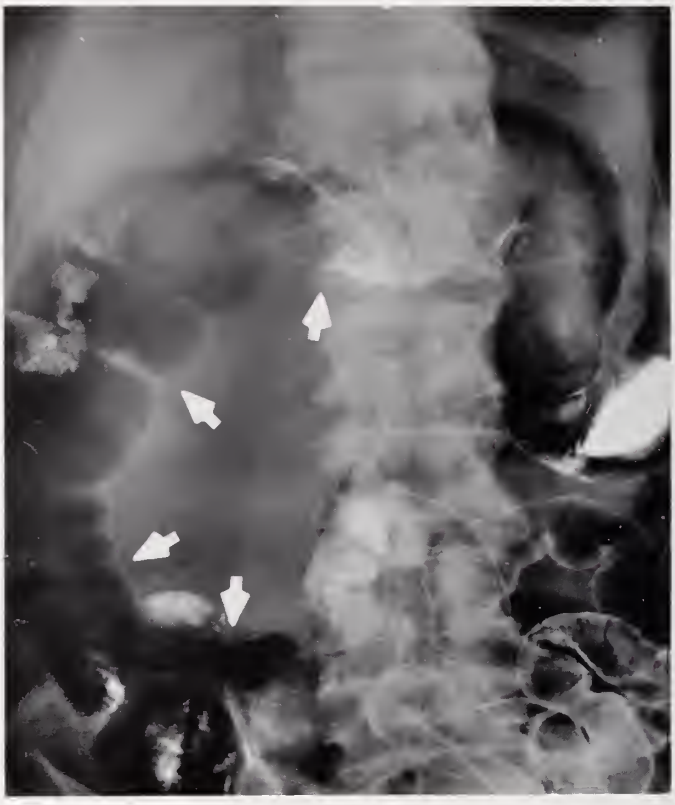

Fig. 2. Anteroposterior view with air contrast shows displacement of the right colon and terminal ileum (arrows). The bowel appears intrinsically normal.

abnormal vessels and a tumor stain were delineated in the lower portion of the mass.

At laparotomy, a large neoplasm was seen to occupy the right retroperitoneal space. The lateral portion displaced the ascending colon. The superior portion extended behind the bowel into the mesocolon and displaced the transverse colon and hepatic flexure. The mass was highly vascular. A biopsy revealed extensive hemorrhagic necrosis. No definite pathologic diagnosis could be made.

Case Report: Malignant retroperitoneal neoplasm with unusual colonic displacement.

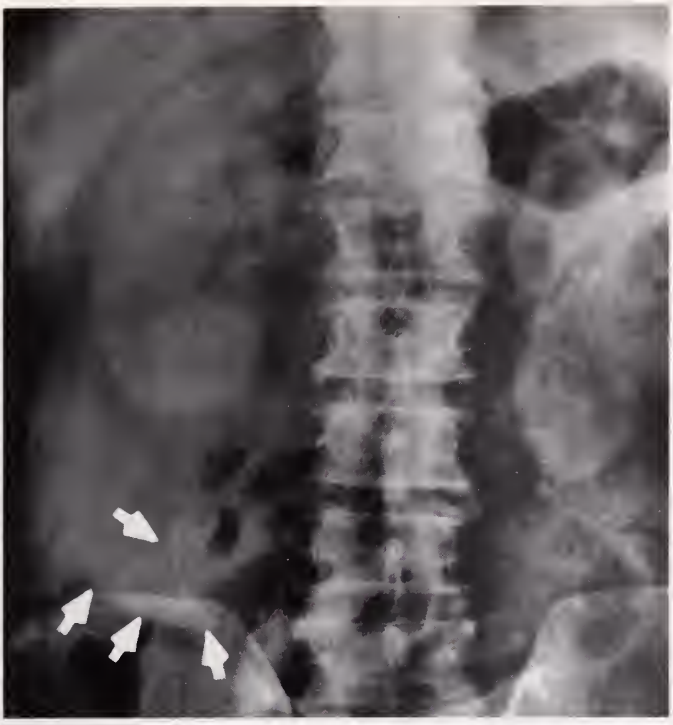

FIG. 3. Nephrotomogram in the arterial phase demonstrates the integrity of the right renal outline. The kidney is elevated, however. The lower border of the mass is well delineated (lower arrows). Abnormal tumor vessels are seen (upper arrow).

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Ralph Colp and Dr. Eric Schweiger.

CASE NO. 201

A 68 year old male was admitted to the hospital with a three week history of progressive abdominal swelling. A moderate weight loss was noted but there was no associated pain or significant gastrointestinal symptomatology. There was no history of trauma.

Physical examination revealed a soft, non-tender, orange-sized mass in the upper midabdomen. No organs were palpable and there was no peripheral lymphadenopathy. Routine laboratory examinations of the blood and urine were normal.

Barium meal examination showed a normal esophagus and stomach. There was evidence of a soft tissue mass measuring 9 cm in diameter which exerted extrinsic pressure on the third portion of the duodenum displacing it superiorly (Fig. 1). The mucosa of the duodenum was intact. A few jejunal loops were displaced inferiorly by the mass. The superior and right lateral contours of this mass were

also discerned. An intravenous urogram showed normal internal renal structures bilaterally. Both upper ureters were abnormal in course (Fig. 2). There was displacement of the upper left ureter laterally and anteriorly and the upper right ureter was slightly bowed medially and posteriorly. Both psoas margins were preserved. Barium enema examination revealed a polypoid intrusion into the lumen of the proximal transverse colon (Fig. 3a). An ulceration of the mucosa was not identified. With the bowel contracted, the mucosal pattern seemed dis-

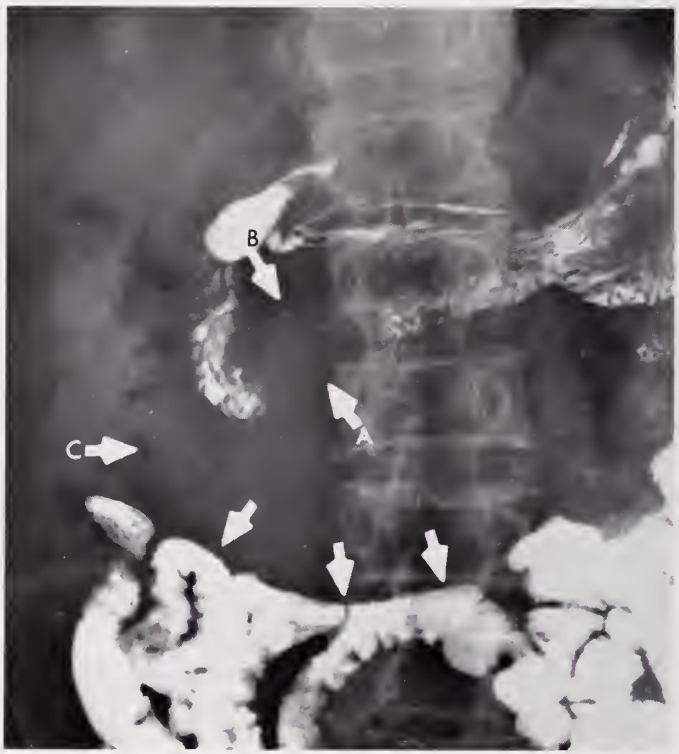

Fig. 1. Abdominal film from barium meal examination shows evidence of displacement of small bowel loops by a mass (lower arrows). Extrinsic pressure on the third portion of the duodenum is also noted (arrow A); this appearance was constant on numerous radiographs. The superior and right lateral contours of the mass can also be discerned (arrows B and C).

torted implying fixation here (Fig. 3b). The findings in the transverse colon were noted to be in relation to the soft tissue mass.

At laparotomy, a well-demarcated, spherical mass measuring approximately 7 cm in diameter was noted within the transverse mesocolon and the root of the small bowel mesentery. The mass surrounded the superior mesenteric vessels and was fixed to the wall of the transverse colon. The retroperitoneal lymph nodes were not enlarged. A subtotal resection of the tumor was performed. The histology was reported as small-cell lymphosarcoma. The patient was referred for radiation therapy postoperatively.

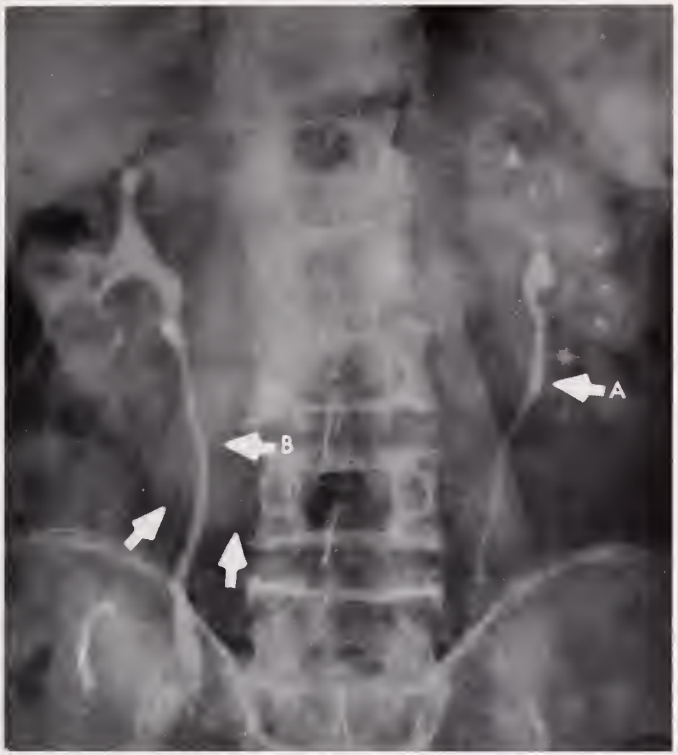

FIG. 2. Intravenous urogram delineates an abnormal course to both ureters. The upper left ureter is displaced laterally (arrow A). The upper right ureter shows slight medial bowing (arrow B). The inferior extent of the mass is vaguely discerned (lower arrows). Note the complete preservation of both psoas margins.

Case Report: RETROPERITONEAL LYMPHOSARCOMA LOCALIZED TO THE TRANSVERSE MESOCOLON AND THE ROOT OF THE MESENTERY.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Moses Swick and Dr. Gerson Lesnick.

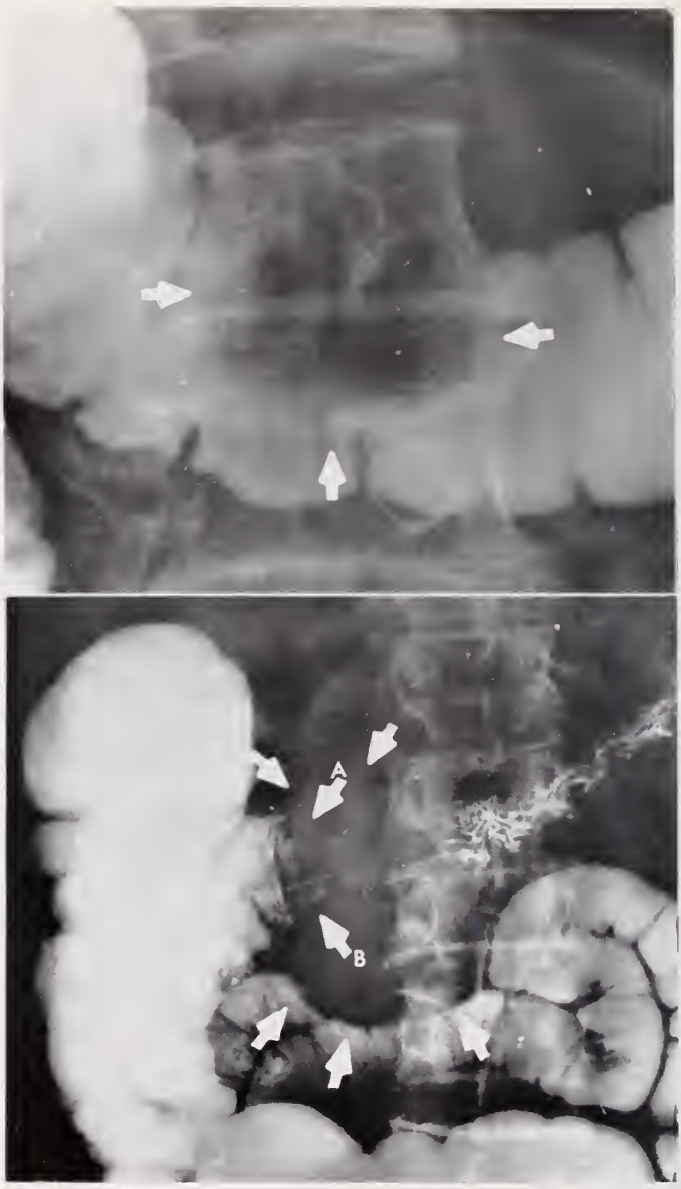

Fig. 3a. Spot film of the proximal transverse colon during barium enema demonstrates a polypoid mass projecting into the bowel lumen (arrows). An ulceration is not identified. The margins are smooth and sharp.

Fig. 3b. With the bowel contracted, distorted mucosa is seen (arrows A and B) indicating mucosal fixation. The abdominal mass is again outlined (upper and lower arrows). The intraluminal component is not delineated.

CASE NO. 202

A thirty-five year old white female was admitted to the hospital with a three month history of progressive abdominal swelling, epigastric pain, anorexia and weight loss.

Physical examination revealed a football-sized upper abdominal mass extending from the xiphoid to below the umbilicus and from the right midclavicular

Fig. 1. Abdominal radiograph from barium meal examination shows displacement and rotation of the stomach upwards and to the right and displacement of the ligament of Treitz across the midline. The upper pole of the left kidney can be discerned. The lower pole and the left psoas margin are obscured.

line to the left flank. The mass was soft but not cystic and was somewhat tender to palpation. Routine laboratory examination revealed a mild anemia.

Barium meal examination (Fig. 1) revealed marked displacement and rotation of the stomach upwards and to the right. The ligament of Treitz was displaced to the right across the midline. The lower pole of the left kidney was obscured as was the left psoas margin. The mass was thus localized to the region of the left kidney and the pancreas. Intravenous urogram revealed a normal right urinary tract with a double collecting system. On the left side, there was delayed

visualization of a dilated portion of the collecting system near the upper pole. The remainder of the collecting system failed to visualize. Left retrograde pyelogram (Fig. 2) revealed a double collecting system with dilatation and distortion of the internal structures of the upper portion. The internal structures of the lower portion were markedly irregular and ragged in contour, typical of neo-

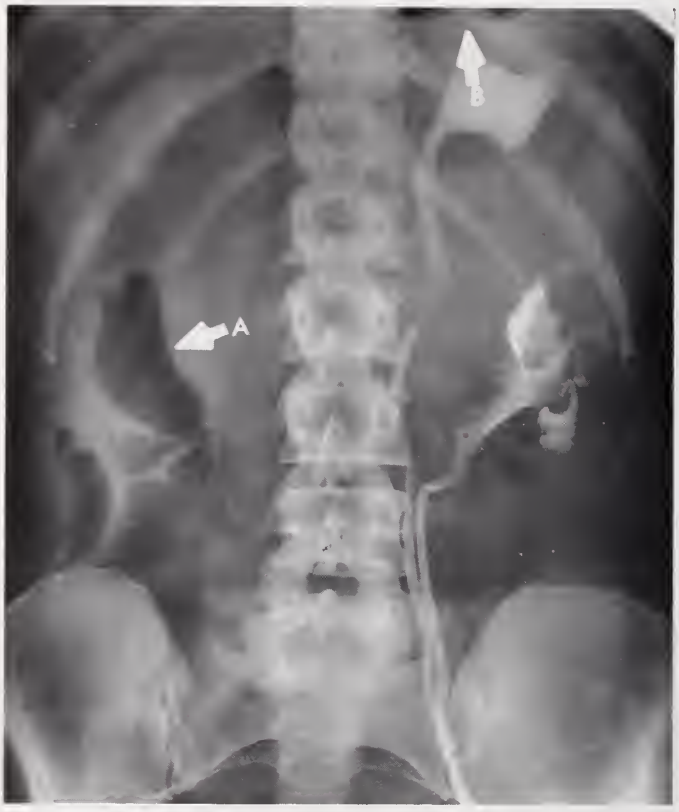

FIG. 2. Left retrograde pyelogram reveals a double left collecting system. There is a ragged, irregular cavity in the lower portion characteristic of infiltrating neoplasm. The upper portion is dilated and distorted. The gall bladder is visualized in the right upper quadrant from previous contrast study. The stomach is elevated and rotated to the right by the large mass. The right lateral aspect of the mass is delineated by air in the gastric antrum (arrow A) and the superior contour is delineated by gas in the fundus of the stomach (arrow B).

plastic infiltration. The X-ray diagnosis was hypernephroma of the lower pole of the left kidney with retroperitoneal extension or lymph node involvement.

At laparotomy a massive tumor of the left kidney was found measuring approximately 17 x 11 x 13 cm. The tumor extended across the midline. The lateral one-third of the pancreas was markedly infiltrated. The pancreas was displaced anteriorly, upward and to the right. No discrete enlarged lymph nodes were palpated. A radical nephrectomy and partial pancreatectomy were performed. Pathologic examination of the specimen revealed a poorly differentiated adenocarcinoma of the kidney.

Case Report: Adenocarcinoma of the kidney with retroperitoneal extension.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Florian Yandel and Dr. A. Z. Freudenheim, Good Samaritan Hospital, Suffern, New York.

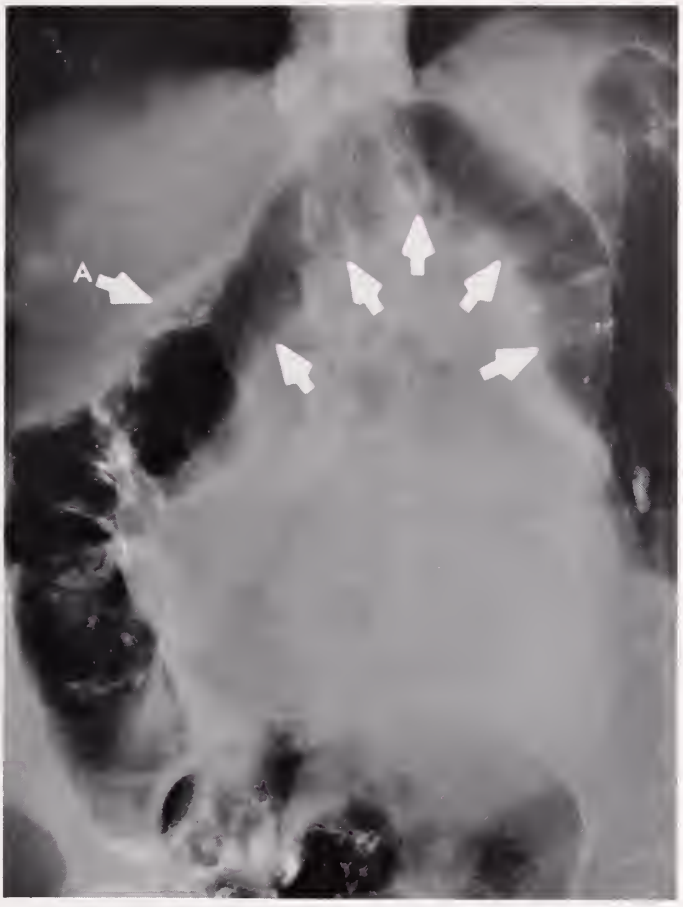

Fig. 1. Air contrast barium enema studies in the postero-anterior projection reveals a sharp upward angulation of the midtransverse colon (along arrows). The cephalad displacement is due to a sharply delineated lower abdominal mass. There are numerous round calcifications in the right upper quadrant (arrow A) which represent gall stones.

CASE NO. 203

A 65 year old female was admitted for an abdominal mass which was diagnosed on routine examination six years before the present hospitalization. Admission was precipitated by a bout of severe lower abdominal pain. The patient had a 15 year history of fatty food intolerance and had been known to have gallbladder calculi.

Physical examination revealed a large cystic mass in the midabdomen, the upper limits of which extended to three fingersbreadth above the umbilicus and whose lower limit extended to just above the symphysis pubis. The mass was soft and not tender.

An intravenous pyelogram revealed no abnormalities of the kidneys or ureters.

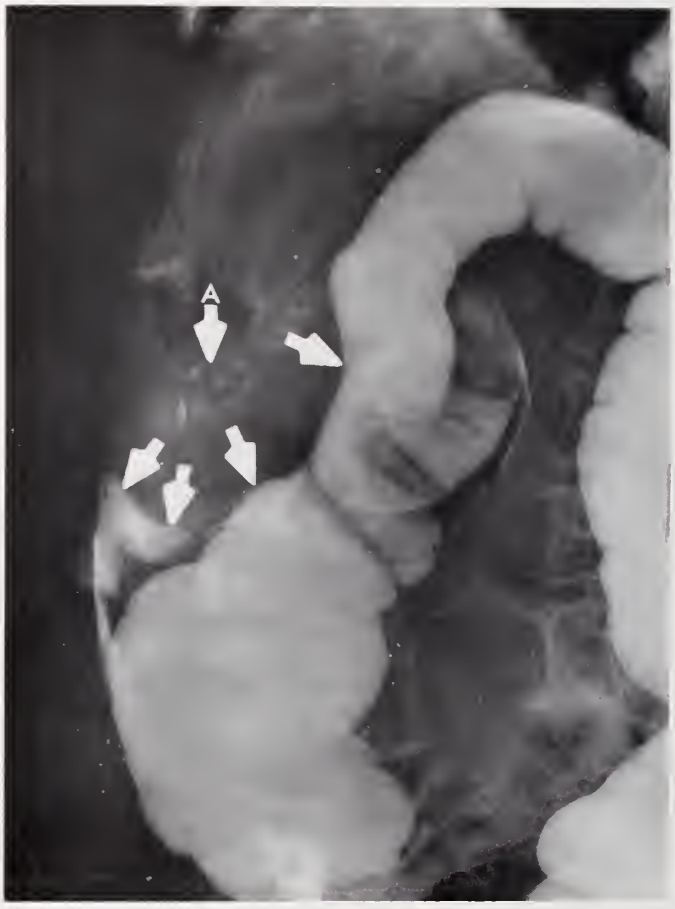

Fig. 2. The barium filled colon in the left anterior oblique projection reveals an extrinsic pressure defect along the hepatic flexure. The proximal transverse colon is displaced downwards and posteriorly and the distal ileal loops downwards (along arrows). The gall stones are again identified (arrow A).

Multiple calcified gall stones were seen in the right upper quadrant. An ill-defined soft tissue mass was noted in the midabdomen displacing the small bowel loops downward. The liver and splenic shadows did not seem to be enlarged. Barium enema examination revealed that the transverse colon was displaced upwards in its midportion by this mass, causing a sharp upward angulation (Fig. 1). The distal ileal loops, which were filled by reflux, were noted to be outlining an apparently separate mass in the right upper quadrant situated anteriorly

(Fig. 2). This mass also caused a pressure defect upon the hepatic flexure. The possibility of a multilobulated cyst or multiple separate masses was raised in view of the simultaneous upward displacement of the midtransverse colon and the downward and posterior displacement of the hepatic flexure with caudal displacement of the distal ileum.

At operation, a large thin-walled cyst 15 mm in diameter arising from the undersurface of the right lobe of the liver was found. Numerous smaller cysts were also seen arising independently from the lower edge of the liver. Multiple small daughter cysts were noted within the walls of the larger cyst. Pathological examination revealed a multilobulated cyst of bile duct origin.

Case Report: Hepatic cysts of bile duct origin.

DISCUSSION

The differential diagnosis of a patient with an abdominal mass depends to a large extent on whether it can be determined roentgenologically if the mass is intraperitoneal or retroperitoneal in location. When the mass is small or moderate in size it is relatively easy to localize because of certain typical behavioral characteristics. Retroperitoneal masses tend to displace the kidneys, ureters and the ligament of Treitz and the psoas margins are often obliterated; intraperitoneal masses tend mainly to displace bowel loops. However, when masses become very large in size as in all the cases presented, these basic rules often are not valid.

In Case No. 198, the large exogastric leiomyosarcoma displaced the ureter and the ligament of Treitz (Fig. 1). Furthermore, in spite of the fact that the tumor was of gastric origin, the transverse colon was displaced upwards (Fig. 4). At first glance this would tend to exclude a tumor of gastric origin. The explanation for this unexpected colonic displacement is the strategic location of the tumor which extended through the transverse mesocolon inferiorly. Its massive enlargement then displaced the transverse colon upwards rather than downwards. It is of interest that the tumor made very little expression in the stomach itself, a characteristic feature of endoexogastric tumors with large exogastric components. Although often enormous in size, the attachment to the stomach is usually by a narrow base. A history of melena as in this case is an important differential point, implying mucosal involvement at some point in the gastrointestinal tract. The marked posterior displacement of the small bowel and colon is also bizarre for a gastric neoplasm (Fig. 3).

The behavior of the large liver cyst, Case No. 203, is similar in one main respect to that of the exogastric leiomyosarcoma. Again the transverse colon was displaced upwards and the mass presented in the midabdomen (Fig. 1). One would have expected a type of colonic displacement comparable to the effect of the smaller liver cyst (Fig. 2). The unusual displacement is explained by the invagination of the cyst through the transverse mesocolon with extension inferiorly. Its subsequent enlargement displaced the colon upwards.

Case No. 201, a retroperitoneal lymphosarcoma located within the transverse mesocolon and the root of the small bowel mesentery, was atypical in its dis-

crete displacement of small bowel loops. The localized effect on the third portion of the duodenum pinpointed its retroperitoneal location (Fig. 1). Its presentation as a filling defect in the transverse colon represented extension into the bowel from the mesocolon (Fig. 3). Although both upper ureters were displaced, the psoas margins were preserved (Fig. 2). This combination of findings is often seen with retroperitoneal lymph node enlargement. At laparotomy, however, the lymph nodes were not enlarged so that the explanation of X-ray findings rests on the well-circumscribed nature of the strategically located tumor. In general, the state of the psoas margins, per se, is not a reliable indicator of tumor location.

Another retroperitoneal neoplasm, Case No. 200, displaced the right kidney without infiltrating it (Fig. 3). However, its maximum effect on neighboring structures was its displacement of the colon (Figs. 1, 2). The tumor, originating in the retroperitoneal space, extended into the mesocolon and thus affected the transverse colon. The displacement of the right colon is more easily understood since this structure is itself retroperitoneal. The malignant nature of the neoplasm was confirmed by the abnormal tumor vessels in the arterial phase of a nephrotomogram (Fig. 3).

In Case No. 199, the exoenteric leiomyosarcoma, it is of interest that the correct diagnosis was made preoperatively on the basis of the roentgen findings. The diagnosis was suggested by the presence of a very large lobulated mass which fixed a single long loop of small bowel and displaced adjacent loops (Fig. 1). A sharp point of angulation with distortion of the mucosal pattern was observed at the proximal end of the fixed loop. This segment was interpreted as the point of origin of the mass.

In Case No. 202, the diagnosis of a renal carcinoma was obvious from the retrograde urogram (Fig. 2). The unusual feature was the marked displacement of the stomach and the ligament of Treitz (Fig. 1). This finding suggested either retroperitoneal extension of the tumor or metastatic lymph nodes. At laparotomy, the pancreas was infiltrated and displaced upwards by the tumor but the lymph nodes were not grossly enlarged.

Thus it can be noted from the cases presented, that many of classical roentgen signs associated with abdominal masses fail to be valid when the tumors reach enormous size. Careful radiological study can nevertheless be of great aid in determining the site of origin and often even the type of these intra-abdominal tumors.

ABSTRACTS

Papers Presented before the Research Club of the Mount Sinai Hospital

New York, N.Y.

Potassium Chloride Induced Diuresis in the Dog. Norman Bohrer, M.D., and Melvin Kalm, M.D.

Preliminary experiments were performed to evaluate the magnitude of a potassium induced diuresis. In 12 of 13 experiments on intact anesthetized dogs in whom a stable rate of solute excretion was attained by constant saline infusion, a slow switchover to an equimolar potassium chloride infusion resulted in an electrolyte diuresis. Sodium, potassium, chloride and bicarbonate excretion were all increased without significant changes in glomerular filtration rate. In order to localize the segment of the nephron from which this excess of electrolyte is derived, studies were performed during maximum antidiuresis and during water diuresis. When a potassium diuresis was superimposed on a mannitol and/or saline diuresis at that rate of solute excretion associated with a plateau or fall in the Tc_{H_2O}, the further increase in solute excretion produced by the potassium resulted in a rise in the Tc_{H_2O}. When solute excretion was enhanced by potassium administration during water diuresis, the increased rate of solute excretion was associated with a fall in free water clearance without a decrease in the rate of urine flow. It is tentatively concluded that: 1) The electrolyte diuresis induced by infusion of potassium chloride is at least in part a result of interference with electrolyte reabsorption in the distal convoluted tubules, and 2) These experiments support the concept that in the dog the urine at the end of the distal convoluted tubules may be hypotonic to plasma at high rates of solute excretion.

The Radioisotope Renogram in Normal Subjects. Richard P. Wedeen, M.D., Marvin H. Goldstein, M.D. and Marvin F. Levitt, M.D.

In order to provide insight into the physiologic basis and range of variation of the renogram contour in normal subjects, the effect on the tracing of changes in urine flow rate, tubular transport, patient position and ureteral obstruction were evaluated. The time of appearance of the peak counting rate (t_p), the peak to spike ratio (P/S) and the percent of the peak counting rate remaining after ten minutes (P_{10}), were utilized to compare the individual tracings and to establish the range of disparity between separate kidneys. At low rates of urine flow, the peak and spike are increased in amplitude, the time of the peak is delayed and steps appear, usually in the third (excretory) phase. This "slow flow" renogram appears to be due to the accumulation in the renal collecting system of small amounts of urine containing concentrated I^{131}-hippuran. The appearance of steps is dependent upon the influence of gravity, the spatial orientation of the ureteropelvic juncture and ureteral motility which produce periodic drainage. Each of the renogram parameters is progressively reduced as urine flow rate is increased.

The dependence of the renogram contour on the rate of urine flow is most marked at very low rates of flow. Competitive inhibition of tubular transport by PAH loading produces a flattening of the renogram contour. The role of tubular transport in determining the amplitude of the first (vascular) phase is indicated by the absence of disparity of this phase after the administration of I^{131}-human serum albumin to patients with a unilateral nephrectomy. The nephrectomy patients show a marked disparity in the first phase after I^{131}-hippuran administration. These findings suggest that when a positive renogram occurs in renovascular hypertension it may be due to the unilateral occurrence of the "slow flow" contour and or impaired tubular transport.

The Immunoassay of Poliovirus Antibody with Poliovirus P^{32}. Robert L. Wolf, M.D., Horace L. Hodes, M.D., Julia Roboz, B.S., and Ruth Berger, M.D. (Supported by grants from the National Institutes of Health, Bethesda, Md. (HE-06546-02, E-2247).

The separation of poliovirus-P^{32} from poliovirus-P^{32}-antibody complex is easily performed by means of paper radiochromato-electrophoresis and radioelectrophoresis. When a mixture of poliovirus-P^{32} and human serum albumin is analyzed by paper radiochromato-electrophoresis, all the radioactivity migrates with the radiochromato-electrophoretic mobility of human serum albumin and poliovirus can be cultured only from the area of radioactivity. When poliovirus-P^{32} and sufficient poliovirus antiserum are analyzed by radiochromato-electrophoresis, a symmetrical curve of radioactivity is present at the origin and represents poliovirus-P^{32}-antibody complex. Poliovirus-antibody, which is demonstrated as poliovirus-P^{32}-antibody complex, has a radiochromato-electrophoretic mobility of globulin. The results demonstrate that a poliovirus binding globulin, which is antibody globulin, is produced in human subjects in response to contact with poliovirus. The poliovirus binding antibody demonstrated in these experiments does not abolish the positive cultures for poliovirus from the poliovirus-antibody complex. The binding by poliovirus-antibody of poliovirus-P^{32}, and the demonstration that the fraction of poliovirus-P^{32} bound to antibody increases when greater quantities of antibody are employed, is the basis for a quantitative immunoassay for poliovirus-antibody. It is possible to demonstrate poliovirus-antibody in volumes of human sera which are $\frac{1}{50}$th to $\frac{1}{100}$th of those employed in neutralization tests by means of this simple, rapid, immunoassay technique. Poliovirus-antibody has even been demonstrated with this technique in sera which presumably did not contain antibody when analyzed by other immunologic procedures.

The Effect of Aldosterone on Electrolytes and on Digital Vascular Reactivity to L-norepinephrine in Normotensive, Hypertensive and Hypotensive Patients. Milton Mendlowitz, M.D., Nosrat E. Naftchi, M.S., Eric B. Bobrow, M.D., Robert L. Wolf, M.D., and Stanley E. Gitlow, M.D.

One half mg of *d*-aldosterone, 21 acetate in sesame oil was administered intramuscularly twice daily for three days to fifteen normotensive subjects and fifteen patients with essential hypertension on a fixed intake of sodium chloride

(7.5 Gm daily). Changes produced by aldosterone in serum and urinary electrolytes and in digital vascular responsivity to *l*-norepinephrine (per cent change in work of vasoconstriction per μg of *l*-norepinephrine infused per minute) were determined. Work of vasoconstriction was calculated from flow and pressure measured during vasodilatation as produced by indirect heat and ganglion blockade and also during vasoconstriction as produced by intravenously infused *l*-norepinephrine. In addition, similar studies were carried out in two patients with renal hypertension and in two with postural hypotension.

The only significant electrolyte change was a decrease in sodium excretion in the normotensive group. Digital vascular responsivity to *l*-norepinephrine was significantly increased from an initial high level by the aldosterone in the essential hypertensive group, but only slightly increased in the normotensive group. These results contrast with those produced by prednisone which increases responsivity in normotensive but not in hypertensive subjects. Aldosterone also increased reactivity from an initial normal level in the two patients with renal hypertension and decreased such reactivity from an initial high level in the two patients with postural hypotension. All these effects may be attributed to an increase in the sodium ion concentration of tissues produced by aldosterone. This would suggest that there is an optimum zone of tissue concentration of this ion. Factors which increase the level of sodium concentration so that it rises above or descends below this optimum zone would thus increase vascular responsivity to vasoactive substances. The possibility of a direct action of aldosterone on blood vessels, however, has not been excluded.

Plasma and Urinary Urate Findings in Myeloproliferative Disorders. Harriet Gilbert, M.D., T'Sai F. Yu, M.D. and Louis R. Wasserman, M.D.

In the normal subject uric acid is derived from three sources: 1) degradation of exogenous preformed nucleoproteins and nucleotides that are ingested, 2) degradation of endogenous nucleoproteins synthesized *de novo* in the body and 3) degradation of purines synthesized *de novo* in the body but converted to uric acid without progressing to nucleic acid formation. In subjects with increased hematopoiesis there is an increase in endogenous nucleoprotein synthesis resulting in elevated serum levels and urinary excretion of uric acid. In the myeloproliferative syndrome a spectrum of types and degrees of hematic cell proliferation is found, ranging from a predominant increase in red cell production in erythremia to a panmyelosis in which there is increased production of red cells, white cells and platelets.

Alterations in serum and urinary levels of uric acid were studied in the various phases of the myeloproliferative syndrome as well as in secondary erythrocytosis, in which the proliferative stimulus is directed solely at red cell production. The cases observed included 15 patients with polycythemia vera with no palpable spleen or barely palpable spleen and no evidence of myeloid metaplasia, 7 patients with polycythemia vera and myeloid metaplasia, 11 cases of "spent" polycythemia with myeloid metaplasia or myelofibrosis with myeloid metaplasia, and 8 cases of secondary erythrocytosis. Seven patients with relative

polycythemia and no evidence of increased hematopoiesis were included for comparison.

Forty-eight untreated subjects were placed on an 1800 calorie diet, low in purines and fat and containing 70 grams of protein a day for one week. Medications were withheld and only subjects with normal blood urea nitrogen levels were included. Two consecutive 24-hour urine collections were made on the 6th and 7th day of dieting. A fasting serum uric acid and complete blood count were obtained on the 8th day. Urine was analyzed for uric acid, creatinine and nitrogen.

Serum uric acid was found to be elevated in 36 of the 41 cases with increased hematopoiesis, as compared to one of seven patients with relative polycythemia. Urinary uric acid levels, despite difficulties in complete collection and variations presumably caused by the presence of undetected impairment of kidney function, were elevated in 36 of 41 cases with increased blood cell production. Urinary uric acid levels were also elevated in all seven cases of relative polycythemia. However, if the total nitrogen excretion is taken into consideration, and the ratio of urine uric acid to total urinary nitrogen is determined, the mean ratio in 40 cases with increased hematopoiesis was 0.074 (0.042–0.126) compared to an expected normal ratio of 0.04 ± 0.01 on the prescribed diet. Ratios of more than 0.06 occurred in 26 of 40 patients in this group. The mean ratio in relative polycythemia was 0.054 (0.046–0.062), 2 cases in 7 having ratios above 0.06.

Hyperuricemia was present in ninety per cent of the patients with increased hematopoiesis. There was no correlation between the degree of elevation of serum uric acid and the level of the hematocrit, platelets or white cells. Generally higher uric acid levels for serum and urine were seen in myeloid metaplasia (whether it accompanied polycythemia or anemia) than in polycythemia vera without myeloid metaplasia or in secondary erythrocytosis. In myeloid metaplasia there exists a combination of an enlarged spleen, hematic cells which are being produced in extramedullary sites and red cells which are abnormal in configuration. Thus an increased turnover of nucleoproteins resulting in increased uric acid formation may be attributable to increased destruction of cells at the sites of production and increased sequestration and destruction of circulating abnormal red cells by an enlarged spleen.

The incidence of hyperuricemia in polycythemia vera was 95 per cent, as compared to reports in the literature varying from 25 per cent to 35 per cent. The high incidence found in this series may be due to the selection of untreated patients with active disease.

The Homologous Blood Syndrome. Howard L. Gadboys, M.D., and Robert S. Litwak, M.D.

Rapid exchange of large volumes of homologous blood during experimental and clinical extracorporeal circulation has resulted in the recognition of a syndrome characterized by sequestration of both erythrocytes and plasma away from the circulation blood volume. The reaction is dose-related. Moreover, its hemodynamic manifestations are influenced by the rapidity and duration of blood exchange. Experimental and clinical data suggest a relationship between the

homologous blood syndrome and 1) postperfusion hypotension, 2) pump fever, 3) postoperative pulmonary congestion, and 4) poor response to perfusion by tiny infants and by patients requiring prolonged perfusion. Clinical improvement in these areas has been achieved by utilizing crystalloid solutions to reduce the amount of homologous blood required.

Electrically Induced Reflexes in Muscles Supplied by the Ulnar Nerve. Studies on Normal and Abnormal Infants and Children. Robert Hodes, Ph.D., and Irwin Gribetz, M.D.

Appropriate percutaneous stimulation of the ulnar nerve causes reflex responses in forearm flexor, hypothenar and dorsal interosseus muscle groups in all normal newborn infants studied at 1–8 days of age. These electrically induced reflexes (EIR's), are recorded by conventional electrophysiological techniques from electrodes placed on the skin overlying the reflexly activated muscles.

All three EIR's are depressed when the infant is asleep. The size of the EIR is markedly increased when the subject rouses spontaneously, or is wakened by light, sound, or tactile stimulation.

Several infants were examined serially (3–4 tests) from birth to 6 months. EIR's become progressively more difficult to elicit as age advances. By about three months of age hypothenar and interosseus EIR's are not present in the normal and at 5–6 months the flexor muscle reflex has also disappeared.

Since the occurrence of ulnar EIR's beyond six months of age is considered abnormal, the test has been applied to different types of pediatric patients. Mental retardation of unknown etiology, Sydenham's Chorea, and Niemann-Pick disease, amongst others, have shown impaired nervous system function, with aberrant presence of EIR's in patients who were over one year of age. The possibility of further use of the EIR as a diagnostic aid is discussed.

A Study of Lipid Metabolism and Arteriosclerotic Heart Disease in Israelis of Bedouin, Yemenite, and European Origin. M. J. Schwartz, M.D.* Mrs Bianca Rosensweig, M. Toor, M.D., Z. Lewitus, M.D. (From Beilinson Hospital, Petach Tikvah, Israel.

The diverse population of Israel affords the possibility of studying the effects of diet and environment on serum lipids and correlating these results with the epidemiology of arteriosclerotic heart disease (AHD). Two hundred and twenty-two age and sex matched Israelis of Yemenite, Bedouin, and European origin were investigated. Yemenites were subdivided into those in Israel less than 12 years ("semi-recent") and those in Israel 15–30 years ("early"). Bedouins eat a lacto-vegetarian diet of 1500–2000 calories daily, semi-recent Yemenites approximately 2500 calories 25 per cent of which are derived largely from unsaturated fat, and Europeans some 3000 calories of which 40 per cent are derived from fat predominately saturated. Early Yemenites have adopted many European dietary habits. AHD is extremely rare in Bedouins and semi-recent Yemenites, infrequent in early Yemenites and common in Europeans.

Lowest weight/height ratios, serum triglyceride, cholesterol and beta-lipopro-

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tein cholesterol concentrations, and the most rapid clearance of orally administered I-131 labeled triolein were noted in Bedouins and semi-recent Yemenites. Highest values were found in Europeans and early Yemenites with AHD and related conditions. Europeans with AHD smoked more and exercised less than others. The family history of AHD was most frequently positive in this group and negative in all Bedouins and semi-recent Yemenites. The diet and environment of the latter two groups may have modified their serum lipids and prevented the development of AHD.

One or more of either the cholesterol, triglyceride, or triolein tests was abnormal in 4.6 per cent of 22 normal Bedouins, 7.2 per cent of 28 normal semi-recent Yemenites, 35.7 per cent of 28 normal Europeans, and 90.9 per cent of 22 Europeans with AHD. The serum cholesterol together with either the triglyceride or I-131 triolein test more effectively screened normal from abnormal subjects than the determination of the cholesterol alone.

In Memoriam

ISRAEL SPANIER WECHSLER

1886–1962

On December 6, 1962 there died in The Mount Sinai Hospital one of its most honored and beloved physicians.

Israel Spanier Wechsler was born in Lespedi, Romania in 1886. At the age of 14 he was brought to this country by his parents. Within only seven years he mastered the English language, completed his preliminary education and was graduated with an M.D. degree from the University and Bellevue Medical College (1907).

By 1917, after a period in general practice, he knew that neurology was to be his life work and was appointed an instructor in neurology at the College of Physicians and Surgeons, an associate in 1919, assistant professor of clinical neurology in 1926, assistant professor in 1927 and professor in 1931. At various times he was neurologist to the New York Neurological Institute, Vanderbilt Clinic, The Montefiore Hospital, and Rockland State Hospital.

In 1938 he rejoined the staff of The Mount Sinai Hospital as Attending Neurologist and Chief of the Neurological Service, a position he maintained with distinction until his retirement from ward service in 1951. At that time he was named Consulting Neurologist.

The first edition of his "Textbook of Clinical Neurology" appeared in 1927 and quickly became a classic. The ninth edition was published before his death. His book, "Neuroses" drew praise from Sigmund Freud and they maintained a correspondence until the latter's death.

His interest in and support of the Hebrew University in Palestine (Israel) dated from 1921 and in this work he was associated with Dr. Chaim Weitzman, first president of Israel, Dr. Judah L. Magnes, first president of the University in Jerusalem and Dr. Albert Einstein. He served on the Board of Governors of the University from 1930 and was deputy chairman from 1950 to 1952. Dr. Wechsler was one of the founders of the American Friends of the Hebrew University, president from 1947 to 1951 and honorary president until his death. In 1959 he was honored by the establishment of the Israel Wechsler chair in Neurology. The University bestowed an honorary degree of Ph.D. upon him in 1955.

Dr. Wechsler was a member of the American Neurological Association (president 1957), The American Academy of Neurology, The New York Neurological Society (president 1934–1936), American Psychiatric, Alpha Omega Alpha and many other societies.

Of all the aspects of his multifaceted career, the one that gave him the

ISRAEL SPANIER WECHSLER, M.D.
1886–1962

greatest joy was the training of young neurologists and a large group of them looked upon him as a loved friend and teacher. He took particular pleasure in the fact that one of his pupils, Dr. Morris Bender, succeeded him at the Hospital.

He is survived by his widow, the former Minnie Wechsler, a daughter, Miriam Wechsler Linn, a brother, Dr. David Wechsler, a sister, Mrs. Eva Lobell and two grandchildren.

Dr. Wechsler died on December 6, 1962, aged 78, of an acute coronary artery thrombosis.

One of the giants of modern neurology, he will be remembered by his many friends and patients as a human being of unbounded sympathy and love of his fellow man and his devotion to all that was good for all mankind.

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Visual Field Testing at the Bedside by Means of Color Plates

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It is well known that the size, shape, and other characteristics of a visual field depend on the method of examination. Neurologists are also familiar with the difficulty encountered in eliciting visual field defects in uncooperative subjects. As a matter of fact, visual field testing is often omitted or considered unreliable in such patients because it is hard to get consistent responses. In view of the role of color, double simultaneous stimulation and figure-ground discrimination in visual testing, color plates were originally used for tachistoscopic presentation in subjects with lesions of the visual system caused by war wounds. They often incorrectly reported the digits corresponding to the side of the visual field defect or omitted them entirely. For example, a two-digit number, such as 56, was reported as "6" or 74 as "4" by patients with left homonymous visual field defects. Even some single numbers were split, with 8 or 9 being reported as "3." Because of these encouraging results, color plates have been used extensively for clinical and experimental evaluation of visual fields during the past ten years, and this method is now a routine bedside procedure on the Neurological Service at The Mount Sinai Hospital in New York (1, 2).

MATERIALS AND METHODS

The color plates are a series of 18 colored figures originally designed for detecting congenital color blindness (3). A typical plate (Fig. 1) consists of a one or two digit number, formed of small colored circles on a background of similar circles, but in a contrasting color. Control of illumination and the exact method of presentation are not critical (but exceptions will be discussed below). Ordinarily, each plate is held up in front of the patient and he is asked to report what he sees. The eyes are tested separately. The first plate of the series consists of an orange "12" on a gray background. It was designed for detecting malingered color blindness, since it can be seen easily by color blind persons. This is also generally the easiest plate for normal subjects to see and it serves to introduce the patient to what is wanted.

If the patient reports no numbers at all, he is asked to name the colors or describe any other characteristics of the plate. If only one digit of a two digit number is reported, the patient is asked to point to the one he sees. If a subject has difficulty in identifying and reporting numbers (as in aphasia, organic mental syndrome, mental deficiency, or in some children) he is simply asked to point to what he sees. If the patient has a refractive error, the tests are performed with corrective lenses. The verbatim replies are recorded. If the patient does not make any errors, the series is repeated *using brief exposure times* (a modifica-

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tion of the test still being evaluated) (4). By this technique, the plate is presented so rapidly that the patient does not report seeing numbers. Then the exposure time is gradually increased until the patient reports at least one number. A similar exposure time is used for the subsequent plates. Another investigation is underway to determine the effect of the color itself upon responses to these plates, by presenting photographic copies in monochrome. They

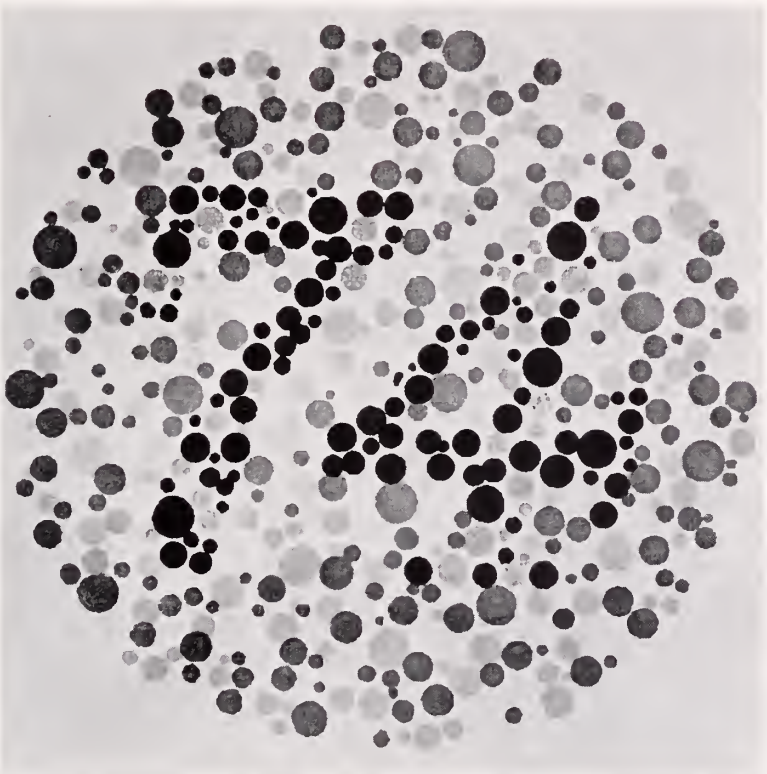

FIG. 1: In the original plate, the number (74) is in greenish-blue circles, the background orange and yellow circles. Left-sided errors are indicated by reports of "4," "24" or "14," right-sided errors by reports of "7" or "71."

may be made into color transparencies and exposed in a slide viewer or by projection on a screen. However, many patients have difficulty in seeing anything in a monocular viewer and presentation on a screen requires equipment that makes the test unsuitable as a routine clinical tool, although both of these methods are useful for experimental investigation.

OBSERVATIONS

Homonymous hemianopia: The patient makes consistent "lateralizing errors" on the side of the field defect. A lateralizing error is one in which the patient reports correctly only one digit of a two-digit number or splits a single

digit. For example, the reporting of an 8 or 9 as a 3, or the reporting of a 3 as an 8 would be considered as a lateralizing error on the left. Reporting 57 as 56 or 52 would be considered as a lateralizing error on the right. Reporting of 57 as 5, or 7 would have the same significance. Sometimes quadrant defects can be elicited, but the test should not be considered reliable for this purpose. Not all patients with homonymous field defects make errors on the plates. The extreme conditions are:

1) A dense homonymous hemianopia to single stimuli, yet consistently normal responses to the color plates, and
2) consistent lateralizing errors on the color plates with no detectable visual field defect on perimetry.

Both have been observed, and possible explanations will be discussed later. Sometimes a consistent pattern of errors will be elicited only after an intravenous injection of amobarbital sodium (5).

Homonymous field defects may often be elicited by this method in uncooperative and aphasic patients, mental defectives and in children who cannot name numbers. The pattern in these cases will be elicited by asking the patient what he sees. If he consistently ignores the digits on only one side, a field defect is almost certainly present.

Bitemporal field defects: The pattern of errors is a bitemporal one. Adult patients with bitemporal field defects almost always make errors on the A-O plates, in contrast to patients with homonymous defects, of whom only 50-75 per cent will show a characteristic pattern. In addition, many subjects, because of associated optic nerve involvement, may not see the numbers at all with one or both eyes. It is in patients with bitemporal defects that it is most important to test each eye separately, since they may perform perfectly with both eyes open.

Optic nerve lesions: Sloan reported in 1942 that patients with optic nerve lesions made errors on the color plates (6). Our own observations have confirmed this. The patient makes errors with the affected eye and not with the other. The more difficult plates (those with poor figure-ground contrast) are at first incorrectly reported, then the "easy" ones, sometimes including the "malingering" plate (12). The errors are usually bilateral or random, although they may show a temporal or nasal predominance. In cases of bilateral optic nerve disease, the errors occur in both eyes (and may be difficult to distinguish from congenital color deficiency). Short of tangent screen examination, this pattern may be the only abnormality on examination of patients with optic neuritis, thus making it particularly valuable for neurologists. Errors on the color plates appear early and disappear late in the course of self-limited forms of optic nerve disease, such as optic or retrobulbar neuritis.

It is now well known that certain neurological signs, including central scotomas, appear in some patients when the body temperature is raised, as by immersion in a hot bath (7). Several patients were given this test using the color plates as part of the examination. Several of them had blurred vision in one eye and could not see the color plates with it, yet reading them normally with

the other. There was a central scotoma on gross testing in each case. After about twenty minutes, the plates again became legible. Optic nerve involvement brought on in this way thus gives the same results with the color plates as when the dysfunction develops spontaneously.

A preponderance of errors in temporal fields should raise the suspicion of a chiasmal lesion and nasal defects may be associated with glaucoma. Papilledema, which may be confused with papillitis or optic neuritis, is not associated with errors on the color plates unless there is also pathology in the visual system in the brain. One patient, aged 12 years, with papilledema, whose blind spots were so large that they could not be distinguished from bitemporal scotomas, read all the color plates correctly.

Organic mental syndrome: In this group the patient may not be able to see any but the easiest numbers. Perseveration is common, so that after having reported 27, for example, several subsequent plates may be reported as 27. In some cases of head injury, inability to see the plates may be the only objective sign of brain involvement. When recovery takes place, the patient again sees all the plates. Pollack has observed the same sequence in patients undergoing electroshock therapy, that is, errors on the color plates during treatment, which were not present before and which disappeared gradually after the treatment was discontinued (8).

Cerebral blindness: In cerebral blindness there is involvement of both right and left visual fields, usually due to bilateral occipital lobe lesions. If the patient is completely blind, of course he cannot see the color plates at all. Upon recovery or in cases of partial blindness, the double homonymous character of the visual field disorder is well shown, since the patient will recover in one half of the field sooner than in the other. Very often, the patient fails to see the left-sided numbers of the color plates, yet makes right-sided errors on other visual field tests, such as double simultaneous stimulation (9).

Ocular diseases: These have not been studied systematically. However, the patient will usually make errors in one eye only or will make bilateral errors with both eyes. In glaucoma, the errors will correspond to the defective portions of the visual field. Since the test number occupies the central 4 or 5 degrees of the field, "key-hole vision" will not necessarily interfere with the patient's seeing the numbers. Two patients with advanced chorioretinitis could see the first plate only (12). Both had very poor visual acuity.

Intoxications: Patients with chronic intoxications with phenothiazine derivatives, barbiturates, d-amphetamine, reserpine and digitalis, have great difficulty seeing the color plates. They typically miss the "difficult" plates (those with little figure-ground contrast). The errors are bilateral. Their relationship to the drug intoxication is established by withdrawing the drug and observing improved performance after a period of time. These chronic intoxications are sometimes difficult to detect, and the performance on the color plates may be an early clue.

Color blindness: Some color blind subjects cannot see any of the plates and no further information can be obtained by this method. However, most color blind

patients can see a few of the plates and their responses to these can be evaluated in terms of lateralization.* The distinction between congenital color deficiency and bilateral errors in both eyes due to acquired disease presents a real problem. In general, color blind subjects will have great difficulty with orange-green plates, such as 57, 74, and 15, and they may report the "confusion numbers." They often miss the "9." Patients with neurological disease do not see the confusion numbers and rarely have trouble with those plates regularly missed by color blind subjects. Extensive studies have not been carried out in this regard and it should be assumed that a pattern of bilateral errors in both eyes is the result of congenital color deficiency unless proved otherwise.

DISCUSSION

The mechanisms underlying the responses of various groups of patients to the color plates are not completely understood. Certainly *color* is an important factor. Lesions of the visual system usually give rise to disturbances in color perception before form or motion recognition are affected. Although some patients who have intact visual fields to small colored test objects will make errors on the color plates, the two are usually associated. Some patients will even make errors on the first plate, designed to detect malingered color blindness (12). This plate was designed so that the discrimination between the figure and background is on the basis of brightness contrast rather than color.† Besides the defects in perception of color, patients with visual field defects often have difficulty with any kind of *figure-ground discrimination*, and many tests of visual function are based on the ability of the patient to distinguish a figure from a confusing background.

The color plates obviously present a complex problem in figure-ground discrimination. Many subjects, even normals, when first presented with the plates claim they cannot see any numbers at all and only after the nature of the test is explained are they able to distinguish the figure from the background. Subjects with organic mental syndrome for example, or with presbyopia, may not see any of those numbers which present relatively little contrast between figure and background. However, reporting only one of two digits in a consistent pattern indicates that the figure-ground relationships are disturbed only on one side, as mentioned previously. This signifies pathology in the corresponding visual pathway. Although the test can be given with unlimited *exposure time*, more errors will occur if the exposure time is reduced. This illustrates the phenomena of *extinction* and *completion*, which are important factors in visual

* Incidentally, in the color blindness plates devised by Dvorine (10), some of the numbers are arranged in order to detect different types of color deficiency. That is, the left-hand digit has a different figure-ground composition than the right-hand digit, so that subjects with one type of color deficiency will miss one digit, and conversely. We are trying to determine whether these plates are suitable for detecting visual field defects, although the characteristics described would seem to preclude their use for that purpose.

† However, if an attempt is made to photograph this plate on ordinary panchromatic film, no number will be seen.

field defects. Extinction is the disappearance of an object in a defective visual field when another object is presented simultaneously in the normal field. Thus the reporting of 5 when 57 is presented is an example of extinction of the digit 7. Extinction may fluctuate in time. In general, extinction has been found to be more pronounced when the exposure time is short. This accounts, at least partially, for the poor performance with brief exposure time. The phenomenon of completion, however, also plays a part. Objects which are actually incomplete may be seen as complete when the defect in the figure is put into an abnormal visual field. For example, in a patient with a right visual field defect, the letter C may be reported as an O, whereas if the C is turned around so that the gap in the circle is in the intact visual field, it will be reported correctly as incomplete. Completion is more likely to occur when exposure time is increased. The factor of completion accounts (at least in part) for the fact that a more recently developed test for congenital color deficiency was not useful for eliciting visual field defects (11). The numbers on the color plates, which are in script and are not written in exactly the same way on every plate, are less likely to be completed than the geometric figures of the newer modification.

Patients with organic mental syndrome and homonymous visual field defects may show the syndrome of *hemispatial inattention*, in which the patient tends to ignore one-half of space, no matter what the stimulus (12). Such patients are unaware of persons standing on the left side, will not recognize auditory stimuli coming from the defective side, will leave food on the plate if it is in the defective field and have difficulty in drawing and reconstructing tasks. Almost all these patients show gross defects when tested with the color plates and many of them fail to see one of the two digits on the "malingering" plate (12). Most of the original studies of the color plates were made on patients with this disorder.

Probably the most important factor in the production of errors is the presence or absence of *involvement of central vision*. This accounts for the great number of errors made by patients with optic nerve and chiasmal lesions, who rarely have mental changes, but in whom central vision is usually involved. When central vision is not disturbed (even though there may be total loss of vision outside the center) patients may have severe visual field defects and normal responses to the color plates. Conversely, in some patients with chiasmal or optic nerve lesions it may be difficult to demonstrate a frank visual defect, yet the predominant involvement of central vision leads to gross errors on the color plates.

SUMMARY

The background, technique, and results in the use of pseudo-isochromatic plates for testing visual fields over the past ten years have been described. The test is simple and can be performed at the bedside, even in uncooperative patients. Since it often uncovers visual field defects which could otherwise be missed, it is suggested as a routine part of the neurological examination. Further studies are being carried out to clarify the underlying pathophysiological

mechanisms which account for the characteristic pattern of errors in this test in patients with visual field defects. We are also studying ways of making the test more useful in bedside diagnosis.

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Internal Structural Correlates with Somatotypes

Part I. Red Blood Cells, Small Veins and Viscera

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Pursuant to a study on normal variation in human cells and tissues begun in 1957, we have looked to various disease entities for clues concerning the significance of normal anatomical vagaries. In schizophrenia (1) we found a probable connection with anisocytosis (irregular size of erythrocytes). In diabetes and coronary artery disease we have found nothing to distinguish the one disease from the other nor from the normal. But, fortunately, we took the precaution of rating the subjects for body build, or rather we had W. H. Sheldon do it for us, and here we seem to have picked up the trail of our quarry once again.

MATERIALS AND METHODS

The subjects of this study were outpatients regularly attending Diabetic and Coronary Clinics.* The group, numbering 99 in all, consisted of 68 diabetic and 31 coronary patients; of these fifty were female (nine of whom were patients with coronary disease; eleven of the total were Negro, two were Oriental. The average age was 62 ± 1 (range 34 to 88 years). Most of the patients were receiving either an anticoagulant or insulin. The blood of each patient was sampled and analyzed by us twice a month for four months. Hospital charts yielded additional hematological information.

Erythrocyte volume was determined by (a) hematocrit and (b) dimensions taken from living cells. The hematocrit method of determining mean corpuscular volume (MCV) is a routine clinical procedure. The counts were made in the old-fashioned way (a Coulter counter not being available) with a Brightline Neubauer chamber and calibrated dilution pipettes, two or three pipettes being used for each determination and the results being averaged. Microhematocrit equipment was employed; precision capillaries (32 × 0.8mm, oxylated) were spun for 7.5 minutes in a Drummond "Microhematocrit" centrifuge. Blood was taken from the fingertip in the case of the diabetics and from the vein in the case of the patients with coronary disease, except that fingertip blood was taken once from each of the latter. We found the fingertip to be the equivalent of the vein as a source of red cells as long as the usual precaution of letting the blood flow freely was observed.

MCV was determined in another way as part of a general survey of cell dimensions, including Price-Jones curves, and the construction of a model of

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the representative cell for each subject. Both wet film and dried smears were routinely made at each sampling. For the temporary wet films, coverslips of 0 thickness, 15 × 25mm, were used with a vaseline seal. Camera lucida outlines of 200 cells, including 50 standing vertically on edge (in order to assess the degree of biconcavity) were completed within twenty minutes of making the wet film slide. For vertical cells, those in rouleaux are unsatisfactory; cells standing upright and alone must be found. Where such cells are not perfectly vertical, the apparent thickness can be corrected by multiplying by the cosine of the angle of the tilt; this angle is determined as follows. The microscope is focused on the upper and lower edges of the cell and these points marked. The distance between marks amounts to the opposite side of a triangle of which the hypotenuse is approximately the cell diameter in the other direction. Twenty-seven degrees was the maximum tilt accepted in the sample, amounting, in such an extreme case, to a 12 per cent correction factor.

Wet film data were preferred to data obtained from smears for the following reasons. A distinct disadvantage of smears for our purpose was the error introduced by drying and fixation. This error is inconsequential clinically, but where small variations in size and shape of the cells are the heart of the project, this error is not only large but to make matters worse, it is capricious. We found that the amount of shrinkage varies from day to day for blood of the same person, and *shrinkage* need not take place. On occasion, the cells are stretched, even when the blood seems to have been handled in the same way. Then, as already pointed out, we wished to inspect the biconcavity of cells standing on edge, and for this, it is hard to imagine a substitute for wet film preparations*. The camera lucida used in this study was a Leitz 45° angle drawing apparatus, which gave no distortion across the field. The optics consisted of a Zeiss microscope with 90× apochromatic objective and 18× ocular yielding 2500× magnification on the drawing plane. Critical illumination from a tungsten ribbon filament lamp was used together with Wratten 58A filter. In order to avoid a sampling error, every cell in each field selected was drawn and measured. Fields were selected on the basis of adequate separation and spacing of cells.

* True, the "pale area" of cells lying flat is a function of the biconcavity, but probably no more than a third of human blood cells have pale areas. We found that if the thickest (t) and thinnest (w) parts of the red cells are measured, pale areas will become increasingly hard to demonstrate as w exceeds $t/2$. (A common range of t, as a mean value of maximal cell thickness for individual person, is 1.8 to 2.3μ, whereas w may vary from 0.3t to 0.8t, or 0.5μ to 2.0μ in absolute values. The membranes approach to within 0.1μ of each other in individual cells, and may be separated by as much as 3.0μ in the case of Mexican hat cells.) Pale areas cannot be demonstrated easily in any of the cells of about 30% of the people we have studied. In these cases mean w exceeds 0.55t. In approximately 40% of our cases the pale areas are conspicuous features of about 5 to 10% of the cells; mean w falls between 0.45t and 0.55t. Only in the remaining 30% of cases, where mean w falls below 0.45t does the blood present the textbook frontal image in many of the cells. Hence the visibility of the pale area is not as much a function of the skill of the microscopist as of the shape of the cell. This means that by a conservative estimate only one cell in three has a pale area by any reasonable definition, even if some kind of paleness can be demonstrated.

Once the physical dimensions of the cells were compiled, it was no problem to calculate volume. The best known formula, that of Ponder (2), is meant for use with dried smears and depends upon the measurement of the pale area (*i.e.* entailing a systematic selection of thin cells only). Having wet film data at hand, we were able to use the following approximation of the solid of revolution of the cross sectional area: the cell is regarded as a toroid having an outer rim of elliptical cross section with a cylindrical midpiece tangent to the inner surface of the torus. (See Fig. 1.)

$$V = \pi^2 ab(d - 2b) + \pi w(m/2)^2$$

where V = cell volume
a = ½ maximal thickness (t/2)

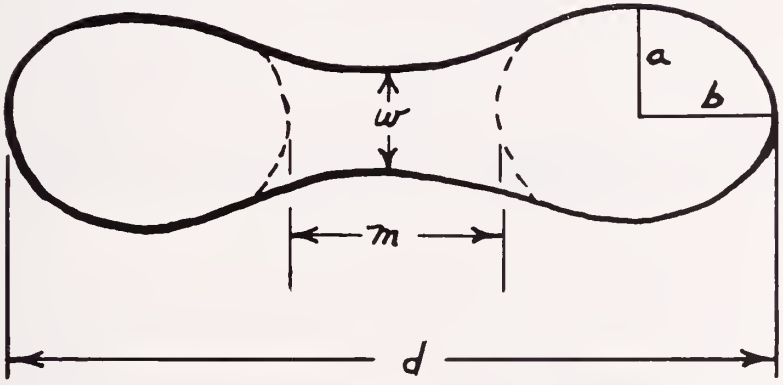

Fig. 1. Schematic drawing of red cell profile showing basic dimensions measured in this study. d = diameter; a = one-half maximal thickness; w = minimal thickness; m = distance between ellipsoids of outer rim.

w = minimal cell thickness (waist)
d = mean cell diameter
b = ¼(d − m)
m = diameter of midpiece. The ellipses of the outer rim are completed and the shortest distance between ellipses measured. The midpiece closely resembles the pale area except that it can be measured in every cell. Pale areas can be substituted for *m* in our formula by subtracting 35% of the pale-area diameter. This correction is not necessary because of any difference in *m* and PA-diameter for a given cell, but because of the sampling error intrinsic to the use of pale areas, which are merely large midpieces.

Mean d, t, w and V were found to be reproducible within five per cent for each subject. That is to say, they seem to be characteristic and identifying traits, varying by no more than experimental error over the period of time covered by the experiment. The deviations in the same individual subject were not such as to alter the subgroup to which he belonged from one determination to the next.

In addition we gauged symmetry and "mechanical fragility" of the red cells. Ovalness, or asymmetry, was measured as

$$\left[\frac{\Sigma(1 - s)}{N}\right]^2,$$

where l and s are the long and short diameters. Mechanical fragility might more appropriately be called *cell fission*. Some red cells have the property of breaking into two or more microcytes of perfect erythrocyte form when sudden pressure is applied to the coverslip of a wet film preparation. Sixty per cent of our subjects exhibited this trait; among college students the incidence is thirty per cent*.

We tested this and every other measure-variable of cell structure against disease, sex, race, medication, blood group, family medical history, general fitness, muscle tone, the use of tobacco and alcohol, and past history of liver malfunction. Special attention was paid to Sheldon's rating of "t" component, both primary and secondary (3). We also rated the fineness of hair and skin from close-up photographs which we took at interview.

Tissues other than blood were taken for study when possible. Biopsies of skin and other organs were collected at surgery when our subjects were operated upon. The viscera of a few cases were measured and weighed at autopsy. The heart was cut open so it could be spread out in two dimensions—measured, traced and weighed. Stomach, liver, lungs and kidneys were traced and weighed. The position of the stomach and the transverse colon were recorded. The subcostal angle and the angle of heart were measured. The length and width of the small and large intestines, the aorta and the esophagus were measured. The thickness of skin and skull were measured and the ranges of variation determined. Photographs were taken before and during necropsy.

Somatotyping

To understand the anthropometric procedure employed, let us apply Sheldon's short method to the subjects presented in Fig. 2. The first step is to calculate the Ponderal Index, or PI ($Ht/\sqrt[3]{wt}$) and the Trunk Index, or TI (Upper Area torso/Lower Area torso) for each subject. We use Sheldon's nomogram for finding PI from height and weight (3) and use a planimeter to obtain the appropriate TI from the somatotype photographs. For subject A the PI is 10.30 and the TI is 1.05. Turning to Sheldon's tables (4) we find the somatotype 7 - 3 - 1 at the convergence of these values of PI and TI. This is the somatotype for subject C. By the same process PI = 10.30 and TI = 1.35 for subject B; these values direct us to the somatotype 6 - 5 - 1. Similarly PI = 12.67 and TI = 1.25 give us the somatotype 4.5 - 2.5 - 3.5 for subject C. Sheldon's tables for short, or automatic, somatotyping are constructed to work for PI's calculated near the maximum weight. This is not necessarily the present weight of

* We assume that there is some connection with age. We have yet to find a person over 75 years old whose blood does not form microcytes under these conditions. Nevertheless, there is no regression with age within this sample, nor with any other trait we could discover.

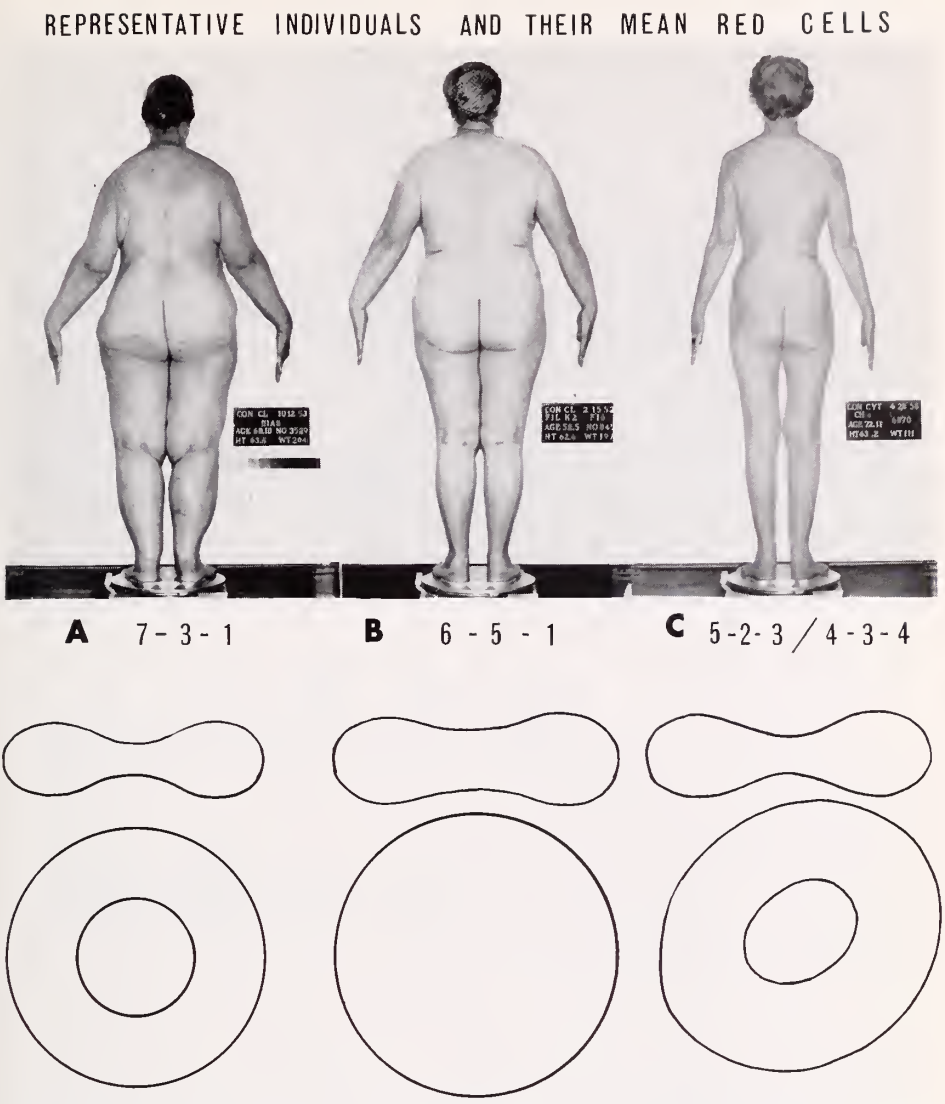

FIG. 2. Each subject is posed and photographed in standardized somatotype posture from three sides. Above are presented the back view of the most endomorphic, the most mesomorphic and the most ectomorphic of our female subjects, A, B, C respectively. The numerals directly below the photographs represent the somatotype; each of the three primary components being rated on a 7-point scale. Beneath each photograph is a drawing of a red cell reconstructed from the mean dimensions of living cells of the subject shown. Note that the endomorph has the smallest cell. The mean cell volumes for A, B and C respectively are $74\mu^3$, $104\mu^3$ and $96\mu^3$. The respective diameters are 7.7μ, 8.3μ and $8.2/8.4\mu$. The respective maximal thickness is 2.0μ, 2.4μ and 2.3μ. The respective minimal thickness is 1.1μ, 1.8μ and 1.2μ. Pale areas were conspicuous features of a few percent of the cells of A and C, but not visible at all in the cells of B. The cells of A and B were quite symmetrical, but those of C were oval.

the subject. We checked the verbal account of past weight history given by the patient with hospital records.

It is desirable perhaps to try to look at the subjects through Sheldon's eyes in order to understand what he looks for in judging physique. At first glance it appears that subjects A and B are quite similar, and indeed the data confirm the fact that they are of about the same stature (about 63″) and show a similar weight history (max. wt. 240 lb). In fact they have exactly the same PI (10.30), which means that they are equally massive. But the TI reveals a different sort of massiveness for each. Subject B has a sturdier frame; at her peak weight she displaced a smaller volume (had a higher specific gravity) than subject A. Note that the skin has not been left sagging despite the fact that she has undergone the same weight loss (40 lb) as subject A. The TI takes the latter differences into account and directs us to quite different somatotypes and corresponding temperamental differences. Each index performs a separate function. PI indicates the linearity (degree of ectomorphy) and TI distinguishes between two kinds of massiveness (endomorphy and mesomorphy) and, incidentally, two kinds of temperament (viscerotonia and somatotonia).

The somatotyping for this study was performed by Sheldon using the photographs and interview sheets we provided. The cell analysis was completed before the information on the somatotypes was available. Sheldon took no part in the cell study and was unaware of the results when he made his somatotype ratings.

RESULTS AND DISCUSSION

What we have done throughout this study is look for new covariance between anatomical and personal traits. For example, when the patients are grouped according to disease (68 diabetic and 31 coronary patients), the cellular characteristics do not show any clear trends. The same is true of sex, race, age, blood group, "coarseness of finish" and all other traits investigated with the sole exception of body build. However, here, several correlations emerge. The patients can be divided into two groups consisting of 52 midrange somatotypes, on the one hand, and 47 predominately endomorphic somatotypes, on the other. The mean red cell diameter (wet film) of the midrange group is $8.00 \pm 0.04\mu$, while that for the endomorphic group is $7.80 \pm 0.04\mu$. ($P = 0.01$ that this difference is due to chance.)

Multiple regression and covariance were calculated for cells and somatotypes using MCV (mean corpuscular volume) and Sheldon's three primary components of physique (endomorphy, mesomorphy and ectomorphy) as variates. The coefficient of correlation is -0.35 for endomorphy. For mesomorphy and ectomorphy, it is about the same, but positive. The R and F values are equivalent to a P-value of less than 0.01. This information is presented graphically in Fig. 3, where the cases are subdivided into four groups in order to demonstrate the regression of MCV with increasing endomorphy. Beside each histogram for MCV, the distribution of somatotypes is plotted on Sheldon's triangular "somatotype edifice." The regression is linear, but may represent merely the linear part of a curve, or nonlinear regression, in a sample where all the somato-

types would be represented. Our sample is deficient in mesomorphic and ectomorphic extremes. Therefore, extrapolations in these areas, where the coefficients are unsupported by actual cases, might be hazardous.

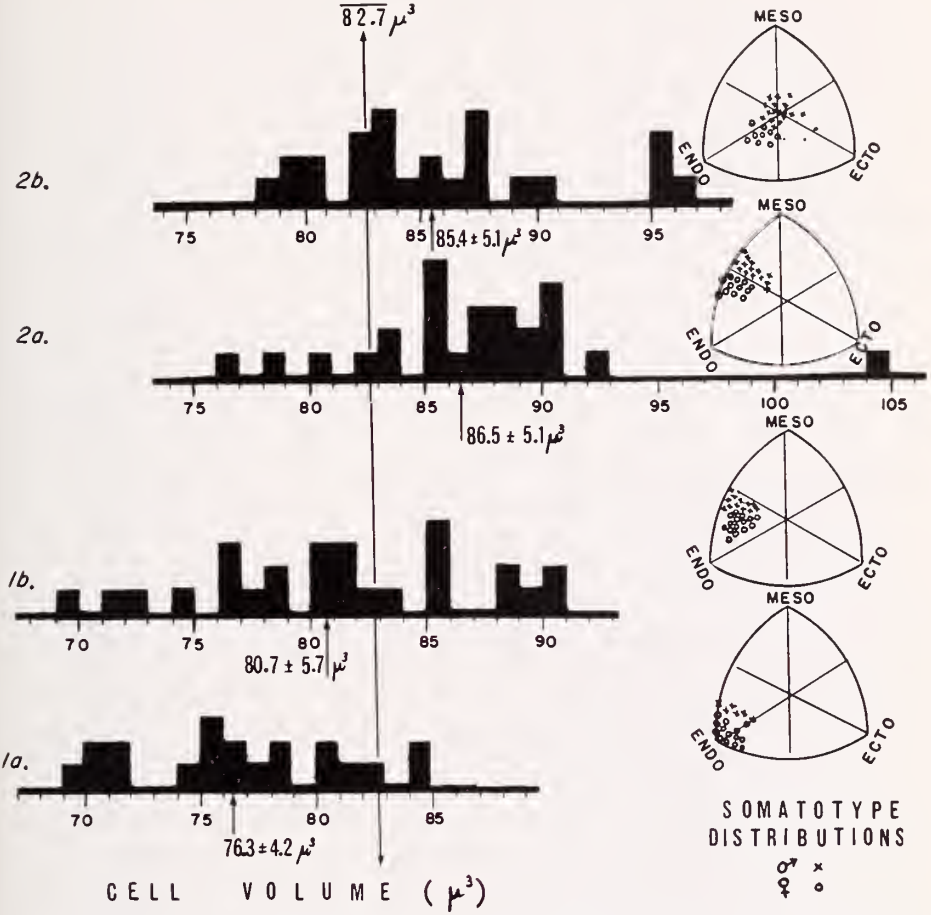

FIG. 3. The sample was organized on the basis of somatotype. Forty-seven predominant endomorphs were placed in Group 1; the remaining fifty-two subjects were called Group 2. Each group was then subdivided into subgroups *a* and *b*. The somatotypes are plotted in the triangular graphs at right. Males and females are shown with separate symbols because the most endomorphic males overlap the second most endomorphic females, and so on. Frequency distribution of mean corpuscular volume (MCV) is presented in the histograms on left. The abscissa represents cubic micra, and the ordinate represents number of cases. The difference of the means is significant if Group 1 is compared to Group 2.

In order to get a better idea of what is producing the significant result, we ran separate covariance with each of Sheldon's key indices, PI and TI. The fit is good with TI (the index which is neutral to ectomorphy and which discriminates between endomorphy and mesomorphy). In Fig. 4 a scatter diagram shows TI plotted against MCV. The coefficient is improved somewhat (to 0.57 ± 0.07) if each sex is fitted to its own regression curve. This complication,

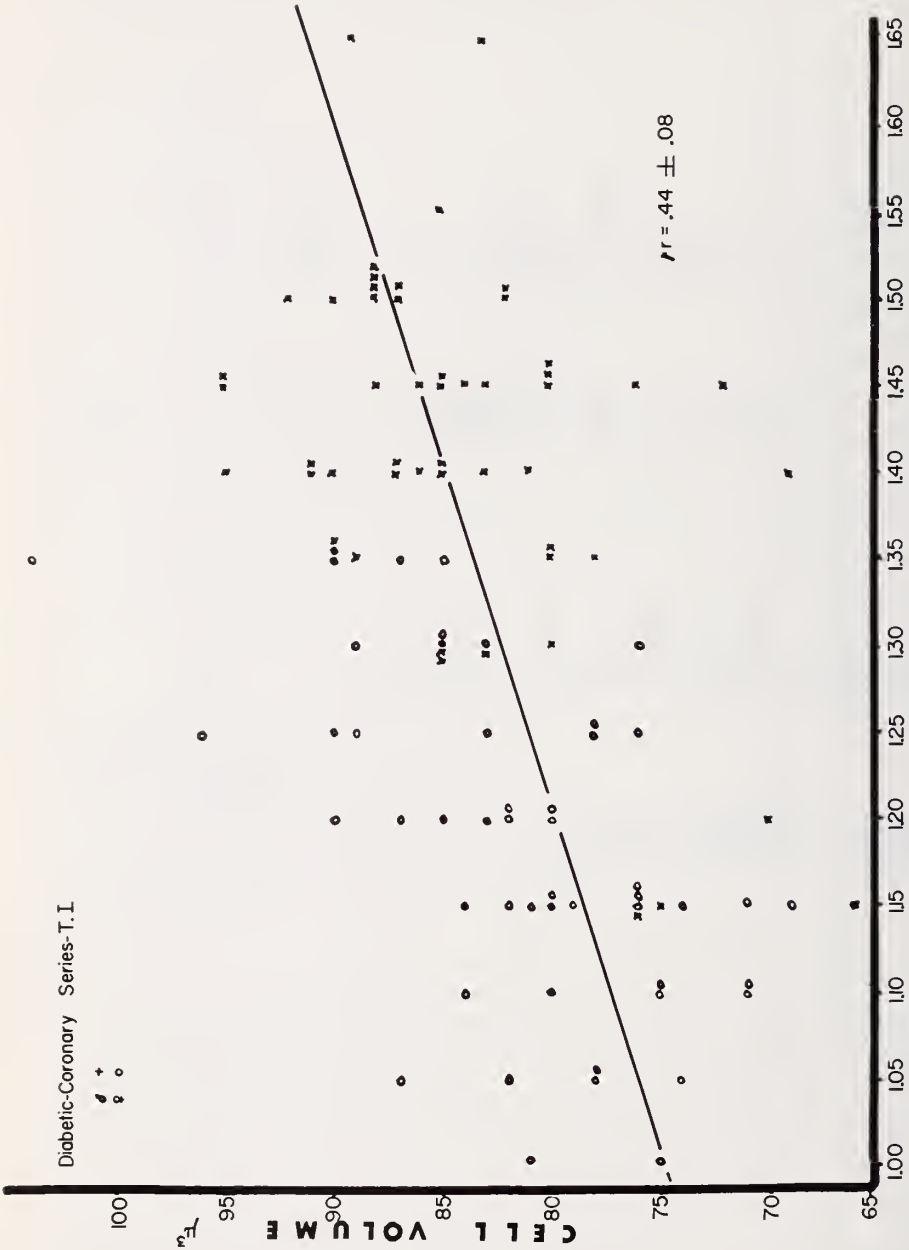

FIG. 4. Cell volume (ordinate) refers to mean corpuscular volume of red blood cells given in cubic microns. The Trunk Index (abscissa) is the ratio of area of upper back divided by the area of the lower back, or buttocks, the line of demarcation being defined by the iliac crests. The regression of Trunk Index with cell volume is significant ($P < 0.01$).

which gives a false impression of a sex difference in red cells, needs further elucidation. For this purpose we briefly digress, as follows. In our sample, males and females have on the average the same sized cells. But the average male somatotype is more mesomorphic and less endomorphic than the average female somatotype. Therefore, even though the influence of endomorphy on cell size is about the same in both sexes, there is a numerical distortion in the calculation, if no allowance is made for the fact that the distribution of female somatotypes is skewed towards the endomorphic pole, as happens when the same physical standards are used for somatotyping both women and men. If "female" standards were to be used for women, the red cell dimensions would follow the same regression curve. However, this is not to suggest that a separate scale be used for women. On the contrary, the adoption of separate scales would make men and women seem more alike than they really are, so that, in the present instance, we might tend to overlook the very curious fact that the sexes converge on cell size although they have diverged on physique, perhaps indicating thereby that women have been more endomorphic and less muscular than men for a very long portion of human evolution.

Price-Jones curves, which visualize the range and distribution of red cell diameter per individual, were repeated on the same individuals. The individual variance was uniformly low throughout the entire sample, the mean being $\sigma^2 = 0.54 \pm 0.08$. This result is in striking contrast to our study of schizophrenia (1). The range of σ^2 among schizophrenic patients being from 0.5 to 2.2 with a group mean in excess of 1.0, almost twice the mean of a normal population as well as that of the present sample of diabetics and patients with coronary disease. Schizophrenic individuals that we have studied since 1957, not included in the present report, have also shown abnormally high variance, emphasizing the significance of the low σ^2 value for this sample.

Cell volume compares favorably with cell diameter in its usefulness for characterizing individuals. The permanence of these properties has been more or less previously assumed, even though there has never been an adequate demonstration that this is so. For present needs, however, it is enough to have shown that average volume and diameter have not varied during the study. In Fig. 5 the relationship of MCV to diameter is presented. The scatter reflects differences in cell shape, *e.g.* cells having a volume of $85\mu^3$ vary from 7.6μ to 8.4μ in diameter in our sample. Data in support of the thesis that cell *shape* as well as cell size tends to characterize the individual are presented in Figs. 6 and 7. Two features of red cells most characteristic of the individual person are cell thickness, especially the minimal thickness (w), and ovalness of outline, or asymmetry. In Fig. 6, w is plotted against TI to show a regression similar to that of MCV. In Fig. 7, asymmetry is plotted against diameter in order to show that the larger cells are generally the more oval, although the same degree of ovalness is sometimes found in the smallest cells. The lower the TI and, conversely, the higher the endomorphy, the narrower the "waist" of the red cells and the more perfectly circular the frontal outline. These characteristic differences in shape are indicated in Fig. 2 where three individuals from our sam-

ple are shown together with their red cell profiles, whose cross sectional reconstruction was determined from the mean dimensions of 200 cells per subject.

In addition to the foregoing material, we had access to the files of the Pathology Department for assessment of whatever tissues had been removed at surgery not only from the subjects of the Diabetic-Coronary series but also from

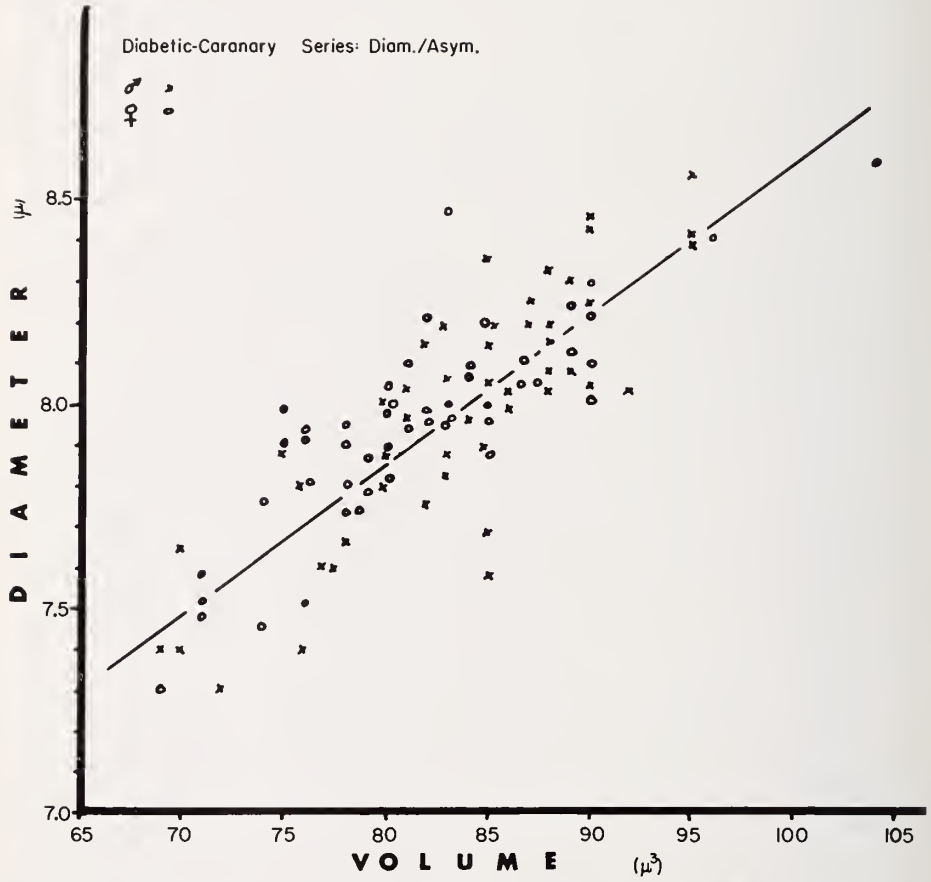

Fig. 5. Cell diameter (ordinate) is plotted against cell volume (abscissa) to demonstrate the linear relationship between two variables which are thought to be persistent and to identify the individual.

any other patients who had been somatotyped. Here, we studied small arteries and veins, since these are usually well represented on most slides. The arterioles proved to be barren ground for our purpose, but not so the venules. Again and again, the venules presented what appeared to be a typical appearance for the individual in question. We located slides labeled normal cervix for twelve different subjects. A systematic comparison of every venule of 300 to 400μ caliber revealed that the more massive the adventitia the more mesomorphic was the subject. The data are presented graphically in Fig. 8.

We also attended autopsies of 22 adults, including six who had died of coro-

nary artery disease, one of these being from our series. From measurements of the gross anatomy, a few trends emerge with respect to somatotype. There was a tendency for endomorphs to present a small muscular stomach (under 50 cm.^{2} lateral area) carried high under the transverse colon, quite in accordance with the observations of Anson (5). The wide thin-walled proximal portion of the small intestine, consisting of the duodenum and jejunum and ranging in length in our sample from 2.5 to 15 feet tended to be short (under 7 feet) in endomorphs. The narrow, thick-walled ileum showed somewhat the same pic-

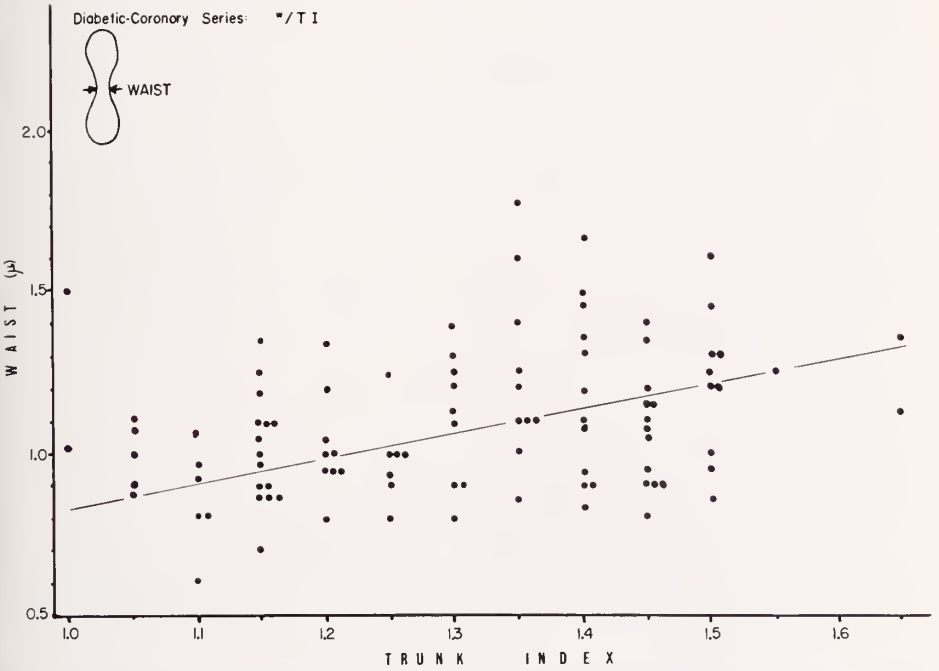

FIG. 6. A scatter diagram shows the regression of red-cell thickness in its most variable dimension (the minimal thickness) versus body build as reflected by Trunk Index. The more endomorphic the physique (low TI) the thinner the cell. Thus, not only size but shape of the cell is correlated with body build.

ture. The longest ileum (23 feet) was found in a fairly lean, flat-stomached extreme mesomorph of average stature; the next longest (17 feet) was found in a mesomorphic endomorph; and the shortest (8 feet) were found in several midrange somatotypes. Yet all but the one extreme endomorph possessed an ileum shorter than 10 feet. Thus, it would appear that for all their digestive powers and bulging forefronts, endomorphs are not overburdened with the physical apparatus for dietary function. This was in marked contrast to the way in which bone, heart and kidney corresponded to relative mesomorphic endowment. The mesomorphs in our sample possessed the largest hearts, lungs, and kidneys as well as the thickest skulls, but the same correlation was not necessarily true of skin. True, the mesomorphs had the thickest skin (7 mm) on

the face and hands, but, in unexposed areas (leg, hip, abdomen, chest and shoulder), these same mesomorphs sometimes had the thinnest skin (under 2 mm), showing that thickness of skin, despite some opinions to the contrary, is not a generalized property of mesomorphs. It would appear that it is the ability to develop such skin that is a mesomorphic trait. Mesomorphs were also found to carry their hearts in the transverse position while the mesopenes (people

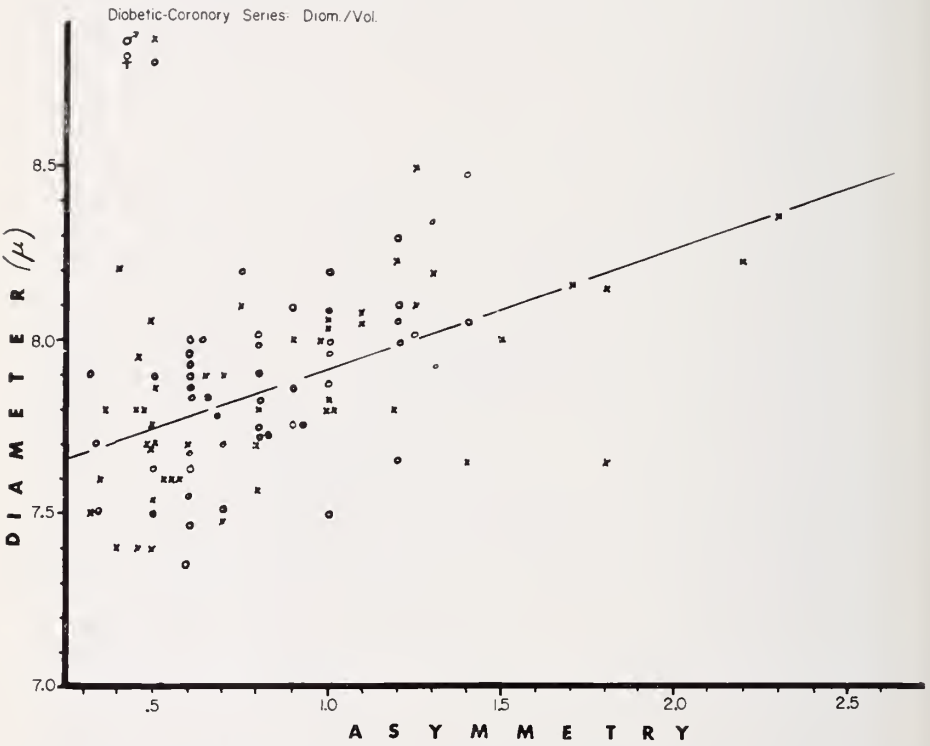

FIG. 7. A scatter diagram shows the sample grouped according to cell diameter (ordinate) from the smallest (7.35μ) to the largest (8.5μ) mean. The mean deviation between long and short diameters per individual subject is squared in order to provide an index of asymmetry or degree of ovalness (abscissa), ranging in the sample from 0.3 to 2.3. There is a trend for the larger cells to be oval shaped, but it is not an obligatory function of size since the smallest cells (below 7.7μ) display almost the whole range of asymmetry. The trait is taken to be a characteristic of the individual person.

deficient in mesomorphy) carried them vertically. The angle formed with the horizontal by the right side of the heart varies from 5° to 50° and presents a good inverse correlation with mesomorphy.

The layer of cutaneous fat at the abdomen ranged from 6 to 60 mm in thickness and rather faithfully reflected the endomorphic endowment. Less than 20 mm of fat meant less than 5 units of endomorphy.

CONCLUSIONS

This is one of those studies that is more often talked about than actually taken in hand and performed. The usual hypothesis, at least on the part of constitu-

tional writers, has been qualitative rather than quantitative, but there have been as many guesses concerning which quality might be involved as there have been constitutionalists. A partial list would have to include strength, health, beauty, longevity, sanity, intelligence, moral character, and will power. As cytologists we could not ask for a better precedent than Boveri's study of a human giant and dwarf (6), in which study he showed that differences in

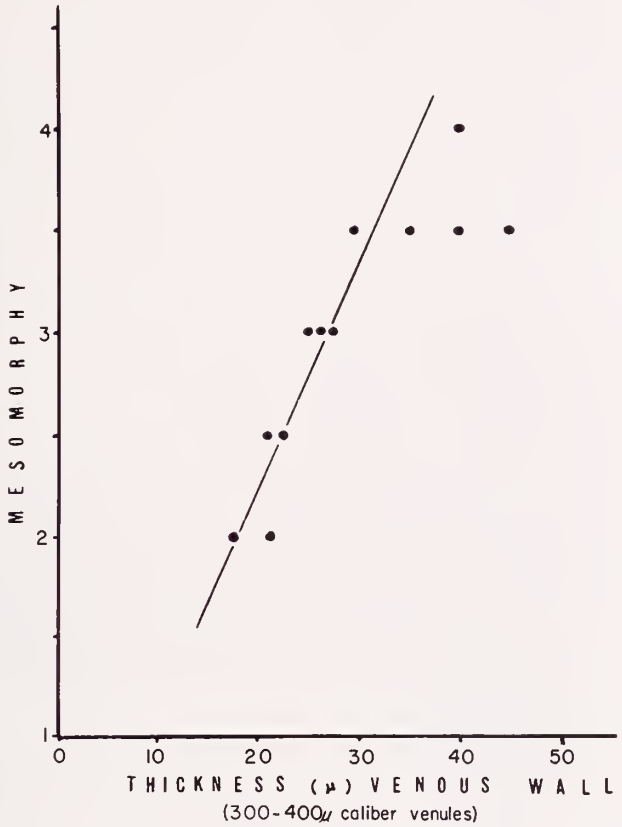

FIG. 8. The thickness of the venous wall (abscissa) is plotted against degrees of mesomorphy (ordinate) for twelve subjects. The tissue in each case was cervix examined by the pathologist and certified as showing no pathological changes. The veins were all of a comparable size, showing a lumen of 300 to 400μ.

stature have little or nothing to do with cell size. In the same period Gulliver showed that the cells of an elephant are no greater than those of a mouse (2).

Until recently, there was a feeling in some quarters that if the tissues of an aristocrat and a peasant could be compared, there would be obvious differences, and moral lessons to be drawn. That was before the aristocrats vanished from the scene or were replaced with play actors. This point of view has persisted, however, in the not quite extinct medical option of labeling cases that are peculiarly unresponsive to treatment as CI's, or "constitutional inferiors." In 1924, Draper (7) proposed the term PPPPT (poor-protoplasm-poorly-put-

together), attributing it to Davenport, and actually tried to produce samples of such protoplasm in tissue culture, with interesting if irrelevant results. Of all the constitutionalists, Sheldon has used the clearest language when he predicted (8) that "two kinds of falling away from good cellular architecture" would be found corresponding to his "blighted and burgeoned estates." However, the only author who guessed right, in view of our present findings, was the hematologist Wintrobe (9) when for no stated reason he ventured the opinion that individual differences in red blood cells are related to body build.

We were looking for peculiarities in the "building blocks," thinking to explain the peculiarities in the "buildings." We forgot that the type of building influences the type of building block used in its construction and that it is not always easy to decide which one is the derivative of the other. Very likely a well-nourished endomorph has less room than average in his small veins and capillaries and less need of strong walls. The red cells may have adapted to the physique. Likewise, mesomorphs lead more strenous lives than average, perhaps for no other reason do they present the classic textbook picture of a vein with all its parts well emphasized. We set out to find a palpable quantity (microscopic) for an ineffable quality (health) and wound up with somatotypes which completed the cycle and left us from where we had begun.

On the way, however, we solved a few puzzles and corrected a few misapprehensions, some being our own. Environmentalists have long entertained the gravest doubts that constitutional differences lie very deep. Yet, if what we have found is true, then Sheldon's primary components of physique can be correlated with structure at the level of the cells. Presumably, his critics will have to assert that the effects of diet and exercise go very deep indeed, if diet is to account for all the differences. For our part we think it more reasonable to admit that there must have been endomorphs for countless ages if there has been adaptation which links endomorphy with the microscopic structure of the body, especially an adaptation so general and widespread that it overrides differences in class, sex, race and medical fate.

Hitherto, the range and diversity of normal red cells has merely been confusing. Possibly the confusion can now be removed by the simple expedient of controlling or, rather, measuring and recording the body build of the individuals used in establishing clinical criteria. Of clinical interest is the fact that the red cells of our extreme endomorphs are small enough to be classified as abnormal (9). Other than the possession of small cells, these people have none of the symptoms usually associated with microcytosis. The subject is complicated because there is a tendency to call endomorphy abnormal in any case (*e.g.* obesity). In order to settle any doubts on the matter, we studied an extreme case hematologically. It was verified that the patient had an MCV below $75\mu^3$, but no diagnosis of microcytosis was forthcoming, nor even considered reasonable, because other than the possession of small cells none of the symptoms usually associated with microcytosis were presented. Again, macrocytosis, an important diagnostic feature of pernicious anemia, is far from being an unknown condition in otherwise normal people. Are macrocytes normal for some people and ab-

normal for others? Are only "macrocytic" types subject to pernicious anemia? Perhaps macrocytosis and microcytosis are clinically significant only when they constitute a dysplasia, as when associated with the "wrong" somatotype. Now that influence of body build is understood, it may be possible to not only to answer these questions but also why some investigators have reported one standard for erythrocyte diameter, while others, equally careful and skilled, report another. In this latter regard it may be worthwhile to exhume some famous examples. Price-Jones and Ponder, each pre-eminent authorities in the field, adopt the respective standards of 7.2μ and 8.5μ. The difference cannot be explained on the grounds of technique alone, since McCormick using Ponder's method sides more with Price-Jones, while Ohno using Price-Jones' method sides more with Ponder (2, 10, 11). These are not the only well-known differences. As painstaking a worker as Osgood reports a sex difference in Portland (12), as does Andresen in Denver (13), while Wintrobe reports none in Baltimore (9). All of this confusion arises, of course, from the fact that mean values for normal people have a range of ± 1 micron, the relative enormity of which may be appreciated from the fact that the whole class of mammals, if we but ignore high altitude types (2), falls inside it. The standard deviation (using Gulliver's data as given by Ponder) for single representatives of fifty species of mammals is 0.6μ. This is less than has been reported by Wintrobe for a similar number of men. Erythrocytes are not as variable as many other human characters confusing to medical practice. The human species is indeed unique in being the most variable.

Lest it be thought that our objective in this line of research is narrowly constitutional, we ought not to conclude our remarks without pointing out that such variability as we have studied is a product of natural selection. And natural selection *is* environment. Thus we have been studying, if you prefer, the long term effects of that infinitely accommodating environment which man has created for himself. Lest it be thought that as biologists we show a narrow concern for our own species, let us say before closing that we are merely curious to find out exactly what can happen to a species (any species) allowed to expand in an environment where adaptive niches are developed at a rate roughly proportional to the capacity of the species to proliferate every possible variant.

The experience that our species is having is of the highest biological interest. It excites an immense amount of scientific attention. The more we learn, for example, about hormones, proteins, nucleosides and the like, the more it looks as though the study of human individuality might become a science in itself, bridging the gap between medicine and biology. There seems to be an increasing tendency, however, to describe deviations from the norm where man is concerned exclusively in environmental terms. This is a fashionable innovation. Biology could serve medicine well at this point by insisting on the importance of anatomy. But instead, biology joins in the revolt. One of the most useful occupations of biology in the past had been the attempt to correlate structure with function. More recently genetics has promoted the idea of classifying one function in terms of other functions, such as blood group, tending to make

it seem unnecessary to subject humanity to "bottle scrutiny" as is done with fruit flies. As a result, a great mass of biochemical information has accumulated without morphologic correlation. Patterns of paper chromatography of normal urines or blood sera are published without regard to the individual associated with each pattern. Correlations with blood groups may be given, but is this enough? Gene frequencies are adequate to differentiate populations; they are not adequate to describe individuals. The elementary anatomy of human individuality ought to come first. What comes instead are less and less revealing systems of anthropometry. Physical traits even more neutral than cephalic index are substituted. Cybernetics may not rescue physiological human genetics at this rate before the "traditional discovery" of the structure-function continuum arrives from an unexpected quarter outside of the academic stream.

The "pure" geneticist has contrived to work almost directly with genotypes. For him the human soma or constitution is understandably removed from experimental reality, if only because little is known of the relative contribution of genotype and environment towards a given human phenotype. Constitution study is often dismissed therefore as an obstruction to progress, almost as though it belongs on the scientific midden heap together with vitalism and the like. Admittedly, there are better organisms than man for laboratory genetic studies, but this is not to admit that constitutional studies are useless, or even backward. The relationship between phenotype and genotype is not as loose and indefinite as some geneticists would have us believe when they discuss the problem of studying man. Regardless of the environment, the expression of a given genotype is bound by reaction norms. Therefore, it should be possible to study phenotypes in an uncontrolled, but not unknown environment, though not so readily as genotypes in a controlled environment. It may not exaggerate the case to call Sheldon's Trunk Index a human reaction-norm of sorts. There is evidence from subjects photographed by Davenport in 1914 and rephotographed by Sheldon in 1954 that Trunk Index does not change. Ancel Keyes' published photographs of conscientious objectors taken before and after starvation also show no change in Trunk Index. The physique changes with time and circumstance; the Trunk Index does not. A similar case can be made for Sheldon's so-called primary components of physique: endomorphy, mesomorphy and ectomorphy. Since the primary components are functions of structural properties, they provide a Linnaean analogy around which to marshal intraspecific biochemical deviations. It seems regrettable that such a system of physical anthropology, which encourages attention to highly variable anatomical features should be shelved in favor of the study of gene frequencies based upon all-or-none traits, thereby, tending to eliminate the genetic concept of reaction-norm from consideration*.

* For example some human geneticists have disparaged the use of eye color because slight differences have been detected in identical twins, *i.e.* slightly different shades of blue. From this fact, Newman argues that eye color should be classed with the environmentally determined traits and adjudged "not a good genetic trait" (14). We infer that the reasoning followed by Newman, though not in his own words, is "If a reaction norm can be demon-

No one could be more aware than we are of the sketchy nature of some of the present findings*, but we think the method, however off-beat it may strike the reader, is, in many respects, useful and closer to historical scientific procedure than the method followed in the great bulk of studies on human variations now being published.

SUMMARY

Individual variability in size and shape of the human red blood cell, determined both by hematocrit and microscopic measurements, is found to be correlated with body build; in particular, extreme endomorphs tend to have small cells, which are also highly biconcave and circular in outline rather than oval. The possibility of establishing universal clinical standards for the erythrocyte and the power to discriminate new dysplasias is discussed. A study of the variation in the thickness of the walls of small veins shows a positive correlation with mesomorphy. Mesomorphy is also correlated with size and position of some of the viscera. Mesomorphs have both the thinnest and thickest skin (in the same individuals). Correlations between endomorphy and the digestive system are also explored. The main bearing of the work is felt to lie not with any of these incidental findings but in the constitutional involvement. An attempt is made to evaluate the broad implications of such a finding for both medicine and biology.

ACKNOWLEDGMENT

We are deeply indebted to Dr. Leonard Ornstein, Director of the Cell Research Laboratory of Mount Sinai Hospital, for his sympathetic interest in this work. We also wish to thank Dr. W. H. Sheldon for somatotyping our subjects and giving us access to some of his clinical data. We also wish to thank the subjects themselves, all of whom volunteered to submit to the study on the strength of their own desire to serve as examples for the benefit of others.

strated, the trait should be thrown out, because it is not hereditary in the pure sense." Of course what Newman and every geneticist knows is that we do not inherit traits but genotypes, the expression of which in the normal spectrum of environments is the reaction norm. Blood groups happen to have one-dimensionally narrow reaction norms, giving an illusion of invariable heredity. The explicit preference for this illusion reflects more than a desire to bring scientific purity to human studies; it reflects the unfortunate tendency to deëmphasize practical considerations of human physical and structural realities in both medicine and biology. This process of deëmphasis is sometimes referred to as an "open conspiracy" against racism. The advisability of involving science in expressions of indignation is dubious to say the least. For our own part we decline to join in any assertion that race is a "myth," nor is it our desire to forget Hitler and the practices of the Nazis. It is interesting in this regard that Sheldon's primary components are the same for every race; even his secondary components fail to differentiate people along racial lines. It would be pointless to try to use somatotypes for Nazi-like purposes. But in the study of man, that problem of problems, where any kind of help is welcome if it can add to our self-insight and understanding, somatotyping for instance might rival psychoanalysis, interpreting temperament in terms of morphology instead of childhood conditioning.

* A follow-up study of mean corpuscular volume in a group including all somatotypic extremes has been completed by us and awaits only statistical analysis before publication.

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A Review of Acoustic Neuromas at The Mount Sinai Hospital

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The decision of when or whether or not to operate on an intracranial tumor usually is based on its location, its type (benign or malignant), whether there is progression, the overall clinical picture and the efficacy of other forms of therapy such as radiation and chemotherapy. The decision is often difficult. In the case of the acoustic neuroma, since it is a slow growing, histologically benign tumor, the decision to operate is seemingly an easier one. However, because of its location the early reports of results of operation were discouraging. This obstacle has steadily declined with improved operative techniques. The mortality rates in large series still range from 8 per cent to 29 per cent, not to mention the morbidity rate which varies greatly (1–13).

We have found that the discussions of morbidity in most of the large series have been limited to specific postoperative defects such as facial paralysis, deafness, corneal ulceration and gait. The percentage of morbidity is rarely given in terms of overall performance of activities of daily living. Also we have come to appreciate that statistics on the long term follow-up, based on the patient's written or verbal reply to questionnaires often may be misleading.

The purpose of this presentation is to re-evaluate the results of operation for acoustic neuroma in light of the experiences at The Mount Sinai Hospital during the past ten years.

MATERIAL AND METHOD OF STUDY

At The Mount Sinai Hospital, from January 1951 to January 1961, 69 patients with acoustic neuroma were seen and 64 were surgically treated. All the charts were reviewed and from them data were recorded such as history, physical examination, laboratory work and (where noted) postoperative and follow-up clinic evaluation. All patients were then sent a questionnaire, asking in simple terms for preoperative and postoperative symptoms, as well as for a comparison of preoperative and postoperative function. Of the 44 surviving patients, 29 responded through the mail.

The next step was to contact both those who replied and those who failed to reply, speak to the patient and at least one close relative by phone, asking for more details and/or correcting generalities and nonspecific answers received in the questionnaires. Forty patients and their relatives were thus queried. The family physician also was contacted regarding four patients who had moved out of town.

Of the 44 surviving patients, 27 were then examined personally either at home, in Mount Sinai, or other hospitals in which they are now confined. Six

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others, who had left the City, sent in medical reports from their neurologists. Through our examination, we realized the inadequacy of correspondence, from a patient or his family, as an accurate measure of follow-up studies.

RESULTS

There were 69 patients with proved acoustic neuroma. Operation was performed on 64 patients, of whom three required two separate procedures for the removal of the tumor. The five patients who had no operation will be discussed in more detail in a later communication. Table I illustrates overall statistics of the subjects in the study. Of the 64 patients who were surgically

TABLE I

Acoustic Neuromas—The Mount Sinai Hospital 1950–1960

Number of patients	69
Number of patients operated on	64
Total operations	66
Number of patients not operated on	5
Operated cases	
Male	26
Female	38
Age range 27–75	

TABLE II

Mortality and Morbidity of 64 Operated Cases

1. Mortality 20—deaths in hospital 16—delayed after operation 4	31%
2. Morbidity of surviving 44 patients—19 totally disabled	43%
3. Gainfully functioning survivors—25 patients	57%
4. Overall mortality and total disability—39 patients	61%
5. Overall gainfully functioning—25 patients	39%

explored, 20 (31%) died: sixteen (25%) in the immediate postoperative period of hospitalization, and four (6%) from four weeks to five years after discharge from the hospital as a result of additional and progressive neurologic deficits following surgery. Of the surviving 44 patients, 19 (43%) are totally disabled and, without constant care either at home or in a hospital, could not survive; 25 (57%) are gainfully functioning and are capable of caring for themselves with little or moderate aid. Ten of these are fully employed in or outside the home as active wage earners or fully-functioning housewives, and five were able to return to their original jobs. (See Table II.)

Since the age of the patient at the time of surgery is often considered a factor in the prognosis, this was investigated. Table III reveals the age distribution of the patients at the time of surgery as well as the number of deaths in each age group. The preponderant distribution of cases, 59%, was in the fifth and sixth

decades of life, with a fairly even distribution on either side of these figures. The mortality rate of each age group ranged between 18 and 35 per cent until the seventh decade, when a 50 per cent mortality was found.

TABLE III

Deaths in Relation to Age

Age	Number of Cases	Number of Deaths
21–30 yrs	4	1
31–40	11	2
41–50	18	5
51–60	20	7
61–70	10	5
71–80	1	0

TABLE IV

Deaths in Relation to Duration of Symptoms

Duration SX	Number of Cases	Number of Deaths	
1 yr or less	19	8	40%
1–2 yrs	10	2	
2–3 yrs	5	4	
3–5 yrs	6	2	20%
5–6 yrs	7	0	
7–8 yrs	3	1	
8–9 yrs	3	0	
9–10 yrs	7	2	
10–23 yrs	4	1	

Table IV shows the number of deaths in relation to duration of symptoms at time of surgery. The initial symptoms, in order of frequency were as follows:

Hearing loss	38 patients
Gait impairment	9 "
Tinnitus	5 "
Fifth nerve involvement (numbness on one side of the face)	4 "
Headache, nausea, vomiting	3 "
Organic mental syndrome	2 "
Vertigo	2 "
Seventh nerve involvement	1 "

The period from initial symptoms to the time of operation ranged between 2 months to over 23 years. Thirty-four patients were operated on within the first three years of symptomatology, with a mortality of 40 per cent; 30 per cent in immediate postoperative period, 10 per cent delayed. Thirty patients were operated on from 3 to 23 years after onset of symptoms, with a mortality of

20 per cent. The preoperative and postoperative disability of the two groups was not significantly different.

Of the twenty patients who expired after surgery, an autopsy was performed on seven. In every patient where death occurred in the postoperative period of

TABLE V

Causes of Death—20 Patients

Post mortem obtained in 7 cases	
1—Died after 6 months of disability	3 × 3 × 2 cm schwannoma in CPA. Compression of cerebellum, cerebral edema, hemorrhagic infarction and ventricular dilation.
2—Died 12 hours after operation	Much subarachnoid blood over left convexity. Cerebellar cavity and cysterns filled with blood. Aqueduct and IV ventricle filled with blood. Shift of medulla from right to left.
3—Died 1 week after operation	Left schwannoma, compression of pons, hydrocephalus. Acute hemorrhage, left parietal lobe with needle tract in vicinity.
4—Died 7 days after operation without responding, 6 days after right transparietal tap	Subdural hematoma—7 × 1 cm—right parietal area. Subdural and subarachnoid blood at operative site, left. Hemorrhagic encephalomalacia left brachium pontis and restiform body. Blood cast in all ventricles. Medulla angulated to right by blood clot. Needle tracts show fresh hemorrhages and transected ependymal vein.
5—Died 12 hours after operation	Large hematoma at operative site. Blood cast of IV ventricle and aqueduct.
6—Died 6 hours after operation	Epidural and subdural hematoma at operative site.
7—Died 1 month after operation 2 weeks post-cribriform repair for CSF rhinorrhea 2 days postop. right frontal epidural hematoma	Uncal and cingulate herniation, right. 2 cm mass right CPA ("total removal"). Fresh and old pontine hemorrhages. Hemorrhagic encephalomalacia, frontal lobe. Subdural hematoma, right more than left.

hospitalization, significant hemorrhagic changes were found (Table V). The clinical features of the non-autopsied patients are given in Table VI.

There was evidence of bleeding episodes in some of the patients on whom postmortem examinations were not obtained. Others seemed to have difficulty in the circulation of cerebrospinal fluids, requiring frequent ventricular and spinal drainage and anastomotic operative procedures.

In evaluating the 44 survivors, it is obvious that some preoperative neurologic

deficits are irreversible (deafness), or are inadvertent after surgery (facial paresis and possible fifth nerve impairment). Table VII illustrates the signs and symptoms of the 64 patients before surgery and after a one to ten year

TABLE VI

Clinical Features of Non-Autopsied Fatalities

8—Died 3 hours postoperatively	Never regained consciousness.
9—Died 3 days postoperatively	Difficulty with bleeding, secondary to hypertension. Ventricular taps showed high pressure. Ventriculogram showed block at aqueduct with hydrocephalus. Re-explored with removal of more tumor and necrotic cerebellum which herniated through dura.
10—Died 2 weeks postoperatively	Massive G.I. bleeding postoperatively and diabetic imbalance. Several laparotomies.
11—Slow downhill course for 6 months	Walking postoperatively, then sudden collapse. Many ventricular and spinal taps, anastomoses.
12—Died 1 day postoperatively	Removal of small tumor—never regained consciousness.
13—Died 2 years postoperatively	In mental institution, for postoperative psychosis and severe neurologic deficit.
14—Died 24 hours postoperatively	In "status epilepticus" never regained consciousness.
15—Died 5 years postoperatively	In nursing home—progressive mental deterioration and neurologic deficits.
16—Died 2 months postoperatively	Many ventricular and spinal taps, mastoid anastomosis.
17—Died 10 days postoperatively	One day postoperatively, had subdural hematoma removed from operative site.
18—Died after 4 years	Progressive downhill course—von Recklinghausen's disease.
19—Died 1 week postoperatively	Multiple seizures, ventricular and spinal taps, EKG changes.
20—Died 1 year postoperatively	Progressive downhill course—many ventricular and spinal taps, anastomoses.

follow-up period. Note that all the patients had hearing loss of various degrees, even if it was not their chief complaint. Of the survivors, all were totally deaf on the affected side. Thirty-four complained of tinnitus, which was "relieved"

by surgery. Two now state that the tinnitus has returned, despite total hearing loss on the affected side. Twenty-five complained of true vertigo. Some described lightheadedness, faintness and nausea by the word "dizziness." None of the patients complained of true vertigo after six to twelve weeks postoperatively, but many had "dizziness," a symptom which we were unable to evaluate satisfactorily. Forty-nine patients complained of gait disturbance and three more had dystaxic gait preoperatively. The complaints ranged from "imbalance," unsteady while walking the deck of a sailboat, to complete inability to ambulate due to ataxia. Of the 44 survivors, the gait of 5 was better, of 11 the same, and of 28 apparently worse.

TABLE VII

Signs and Symptoms of 64 Patients before and after Operation

	Preop of 64 Patients		Status of Postop 44 Survivors after 1 to 10 year follow-up		
	C	S	Better	Same	Worse Excluding Deaths
Hearing	64	64	0	—	44
Tinnitus	34	—	"34"	2	—
Vertigo	25	—	?	—	—
Gait	49	52	5	11	28
Facial	5	26	0	5	38
V	21	42	0	5	38
Diplopia	3	3	0	3	14
Nystagmus	0	55	0	21	18
					(19 Totally Disabled)

C = Complaint
S = Sign on Physical Examination

Only 5 patients complained of facial paresis, but 26 were found to have this preoperatively. Postoperatively, none of these improved, 5 remained unchanged and 38 have increased facial paresis, usually total. Of these, 17 had no facial weakness preoperatively.

Symptoms and signs referable to the fifth nerve were reported in 21 patients, manifested by numbness. On examination, however, 42 patients had evidence of fifth nerve deficit usually decreased to absent corneal reflex and/or slight hypesthesia to pinprick. Postoperatively, none improved, 5 remained the same and 38 (16 of whom had no fifth nerve involvement preoperatively) became worse, often with complete loss of sensation in the distribution of the fifth nerve.

Three patients with diplopia preoperatively did not improve and 14 new complaints resulted postoperatively. This was due to sixth nerve paresis or brain stem dysfunction. It is of interest that no patient complained of oscillopsia, although nystagmus was present preoperatively in 55 of the patients. We have

no definite information that the appropriate questions pertaining to oscillopsia were asked.

Added to each of the figures in the extreme right-hand column under "worse" should be the number 20, representing the twenty patients who expired. Nineteen of the patients in the "worse" column are totally disabled. By totally disabled we mean that the patient is confined to bed or wheelchair or requires the help of an attendant to ambulate, get out of bed, dress and/or fulfill his feeding and toilet requirements. Of the 25 who are gainfully functioning, most are worse in all categories of symptoms, but are able to carry out the activities of daily living without the aid of an attendant.

Twenty-five patients had papilledema. There was no distinct correlation between this group and the group of 14 patients with elevated CSF pressure on spinal puncture. Of the 25 patients with papilledema, 3 died in the immediate postoperative period of hospitalization and 4 died after three months to five years of postoperative survival; 4 patients were totally disabled and 14 were gainfully functioning. The mortality in this group was 28 per cent, overall mortality and morbidity was 44 per cent, and the percentage functioning well postoperatively was 56 per cent. These figures show that papilledema did not play as ominous a role as might be expected in prognosis. Papilledema was noted anywhere from 3 months to 23 years after onset of symptoms. This group did as well as the overall series.

We could find no correlation between size of the tumor as seen by X-ray or described by the surgeon, and duration of symptoms, nor could we correlate this in any way with the outcome of the procedure. Some, with early diagnosis and minimal symptoms, had huge tumors; others with prolonged symptomatology had small tumors. Some patients with small and easily removable lesions died; others, with huge tumors, did well. Table VIII shows the diagnostic studies performed. Notably lacking are reports on audiometry. Only a few appeared on the charts, some were performed prior to hospitalization but results were not readily available. The evaluation of deafness postoperatively was made by gross testing.

Of this series, 54 patients had lumbar punctures. The results were as follows: 14 showed opening pressure of 220 mm of water or above; 51 showed protein elevation, ranging from 70–700 mg%; 3 showed protein below 55%.

Fifty-one patients had electroencephalograms: 12 showed bilateral symmetrical slowing and 6 showed bilateral slowing with focal abnormality on the side opposite the lesion. The remaining 33 records were normal.

Sixty-two patients had caloric examination: 56 showed absent vestibulo-ocular response on the affected side; 5 showed minimal responses on the side of the lesion as compared to the opposite side; 1 had a normal caloric response on the initial examination. One week later no response could be elicited. In only eight cases is mention made of absent response in the contralateral vertical canal.

Sixty-two patients had plain skull X-rays, including special views: 16 showed erosion of the internal auditory meatus; 8 showed a widened auditory canal.

Seven had ventriculograms, of which two were diagnostic. Twenty-seven had pneumoencephalograms, of which 24 were diagnostic. Eight had pantopaque instilled into the fourth ventricle and aqueduct, via the lumbar route, of which seven were diagnostic.

There was no instance of an untoward reaction as a result of lumbar puncture, pneumoencephalogram or myeloencephalography. This included patients with papilledema. It should be noted that the pneumoencephalogram proved the most valuable of all X-ray procedures when plain X-rays were normal.

TABLE VIII

Diagnostic Studies—69 Patients

Procedure	Number of Cases	Results
L.P.	54	14 Elevated pressure 51 Elevated protein to 700 Mg% Greatest frequency 100–250 Mg%
EEG	51	18 Abnormal
Plain X-ray	62	24 Abnormal 16 Erosion 8 Wide canal
Calorics	62	56 Absent 5 Depressed 1 Normal caloric with no systemic response
Ventriculogram	7	2 Diagnostic
PEG	27	24 Diagnostic
MEG	8	7 Diagnostic
V. Angiogram	3	2 Abnormal

There are many other manifestations of disability occurring preoperatively, which are more sporadic. The incidence and severity of these, such as dysphagia, dysarthria, severe upper or lower extremity dystaxia, hemiparesis, and hemisensory syndromes, are much increased postoperatively, and may be responsible for the ensuing disability. A common postoperative problem was the appearance of psychoses and severe neuroses. Three patients were committed to mental hospitals because of postoperative psychosis. There was almost always a depressive reaction. The women, somewhat more than the men, suffered from the disfigurement of the facial paralysis; the men suffered because of inability to return to work or to be active participants in events in or out of the house. At least fourteen of the survivors, many of whom are now gainfully functioning, confined themselves to their homes for periods of one to three years postopera-

tively because they did not want to be seen in public; in five, the depression was severe enough to warrant electroshock therapy.

The complications of corneal ulcerations were frequent, requiring tarsorrhaphy in a majority of the survivors (25). Ten patients complained of severe eye pain. Thirty-three have decreased visual acuity in the ipsilateral eye secondary to corneal disease. Twelve patients underwent either spinal accessory or hypoglossal-facial nerve anastomoses. There was no remarkable difference between the facial appearance of this group and the unoperated group. Among the operated patients, no evidence of really useful added function was reported by the patients; some could ripple the corner of the mouth and partially close the eye, but in only one case could the tarsorrhaphy be eliminated because of return of orbicularis oculi function. Patients with hypoglossal anastomosis were plagued by synkinesias of the face and tongue on chewing movements (which further added to cosmetic defect), and by increased difficulty in getting food out of the gingival-buccal cul-de-sac on the paralyzed side. Those with spinal accessory nerve anastomosis had less trouble with synkinesiae of the face (since the shoulder is relatively immobile in regard to facial and tongue movements) and could train themselves to perform more symmetrical mouth movements.

Of interest to note are three patients who subsequently developed myoclonus of the palate. It has been noted previously that lesions of one cerebellar hemisphere, particularly in the region of the dentate nucleus, may subsequently result in the development of myoclonus of the palate (14). Where part of the cerebellar hemisphere is sacrificed at operation subsequent palatal myoclonus may develop.

DISCUSSION

The facts presented here suggest the following:

1. Although there has been considerable refinement in the operative technique for acoustic neuroma in the past few decades, with a resultant significant drop in mortality, the rate remains relatively high. The mortality rate in this series was 25 per cent (immediate postoperative period). The major reason for this probably is not the surgical technique but rather the precarious location of the tumor. The statement that since an acoustic neuroma is histologically benign it should be surgically removed, is an oversimplification of the problem. Also the impression that early recognition followed by prompt surgical removal affords the best results was not borne out in this study. The greatest percentage of postoperative deaths occurred in patients whose tumor was discovered and operated on relatively soon after onset of symptoms (within three years). Others with symptoms of many years' duration and gainfully functioning for the greater part of this period, had the same or somewhat better chance of survival after surgery as did those with the short history.

2. The postoperative morbidity rate in terms of activities of daily living also was relatively high and together with the mortality rate, was quite formidable. It is important to consider the overall morbidity aside from the expected neurological deficits such as deafness, facial paralysis, corneal ulcera-

tion and dystaxia. Of the survivors, 43 per cent were subsequently unable to carry out the activities of daily living unaided. We found that such evaluations could be determined adequately only by personal interview and examination. Questionnaires alone proved to be significantly unreliable. The questionnaires did, however, demonstrate in a number of instances the tendency toward denial of illness on the part of the patient and at times of a relative. An answer such as "feeling great" proved to be on examination part of a euphoric state with denial of grossly demonstrable defects. A reply "better than ever" was found to mean better than his status the first week after the operation. The positive answer to the question of employment was revealed, in several instances, to be a perfunctory job given to the patient by a sympathetic relative for purposes of morale. We found in other patients, usually depressed, that they could perform certain activities that were denied on the questionnaire.

The problem of when or whether to operate cannot be solved with an overall statement. The data presented also do not help solve the problem, but do, we believe, point up the inadvisability of making an "automatic" decision to operate simply because a benign acoustic neuroma has been demonstrated clinically. Perhaps watchful waiting is best for a particular case. The size of the tumor or subsequent development of papilledema, which may never occur, did not seem to affect the chances of survival in this series. The rapidity of the development of deficits with accompanying impairment in gainful functioning is probably the most valid criterion for operation. Age is an important factor, but we found it difficult to determine whether or not operation of the younger person is advantageous in terms of his or her remaining productive years. Of those over the age of seventy it is obvious for many other reasons that surgery is a greater risk.

An explanation for why some series have lower or higher mortality rates is that one or several neurosurgeons performed the operations in a given series. We are not in the position to evaluate the significance of this explanation. In the present series, the patients were operated on by several neurosurgeons. No one surgeon had significantly better or worse results than the others.

We are fully aware that this series of 64 cases is not nearly as large as other series reported, and that the mortality and morbidity in terms of percentage appear relatively high. However, this is also true for survival rates. The recent series of Pool and his associates shows a steady decrease in the mortality rate of their more recent cases, but there is little information as to the overall morbidity in terms of gainful function.

3. This survey gives further support to the mounting evidence that lumbar puncture and pneumoencephalography are of no greater hazard than the alternative, ventriculography, in suspected posterior fossa tumors and, in addition, reveal more information. Where filling of the third and fourth ventricles and the recesses with air was incomplete or equivocal, we found myeloencephalography (pantopaque instillation into the third and fourth ventricles via the lumbar route) to be very helpful in sharply delineating the tumor shift.

SUMMARY

A review of 64 patients operated on for acoustic neuroma at The Mount Sinai Hospital during the past ten years is presented. The preoperative clinical and laboratory pictures were analyzed in light of the mortality and morbidity rates. Emphasis was placed on personal interview and follow-up examination rather than reliance on the questionnaires with all their pitfalls. The morbidity in terms of performance of activities of daily living (gainfully functioning) was evaluated in addition to the commonly expected neurological deficits following surgery.

The morbidity and mortality rates were relatively high. The various correlations with factors such as age, duration of symptoms prior to operation, neurological signs at the time of operation and size of the tumor at operation, did not fully support the general impression that since an acoustic neuroma is "benign" it should be surgically removed or that early discovery and operation affords the best results. Although the tumor is histologically benign, its location is "malignant." There is no doubt that at present, surgery is the only available treatment. However, the question of when or whether or not a patient should be operated on at a particular time, in our opinion, remains unsettled.

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Multiple Primary Malignant Neoplasms

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Progress in all fields of medicine and improved general and social conditions have increased life span considerably. With the increase of life span it is no longer uncommon to see patients with different multiple primary neoplasms. Advancement of modern anesthesia and refinement of surgical techniques make surgery possible in many people in the old-age group, permitting early diagnosis and often cure. Physicians today are becoming more aware of the possibilities of multiple primary malignancies in the same patient. In a recent review Werthamer, Jabush and Schulman reported the case of a patient with four distinct primary malignant neoplasms (1). In 1932, Warren and Gates reported an incidence of 1.84 per cent of multiple malignancies (2). They performed 1078 postmortem examinations on patients with malignant disease and found only three cases of triple primary malignancies originating in three different organs. Quadruple primary malignancies are, of course, even rarer.

In an attempt to ascertain the statistical frequency of quadruple primary malignant tumors, Werthamer *et al.* (1) insist that each case conform to the following criteria:

1. The malignancies must be primary in different organs
2. Paired-organ primary malignant tumors (synchronous or metachronous) would be considered as representing one single tumor
3. Multiple malignant tumors originating in the same organ are considered as a single primary malignancy
4. The lower intestinal tract, as well as the uterus, are considered single organs
5. The malignant nature of the neoplasm must be confirmed by histologic evidence in the organ tissue
6. It must be excluded by careful histologic study that the neoplasm does not represent a metastatic growth.

Conforming to the above criteria, we report the following case as an example of a patient who at various stages of his life had four distinctly different unrelated primary carcinomas.

CASE REPORT

H. F. is a white male, now 83 years old. The patient was first admitted to The Mount Sinai Hospital in 1940 at the age of 61, with a history of weakness, tiredness, anorexia, weight loss and pallor for the previous two months. Physical examination revealed a husky but pale white male. Physical examination was essentially negative except for a systolic murmur heard over the precordium. The abdomen was unremarkable and so was the remainder of his physical examination.

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The patient's hemoglobin was 79% with a red blood count of 3,900,000. The stool was 4+ guaiac positive and there was no free acid in the stomach. Barium enema was normal. The gastrointestinal series revealed a superficial irregular filling defect involving the lesser curvature of the stomach in the region of the antrum and body. The appearance was that of a neoplasm. On September 14, 1940, the patient was explored. A large, movable saddle-shaped carcinoma was found occupying the antral portion of the stomach. There was no evidence of metastases to the liver, pre-aortic or portal glands. The pathology report showed an infiltrating adenocarcinoma of the stomach. No involved lymph nodes were found. The patient was discharged in satisfactory condition on the 21st postoperative day. He was followed regularly in the Out-patient department and has had no further gastrointestinal difficulties for the past 22 years. An upper gastrointestinal series (May 24, 1962) showed a normal stomach status postsubtotal gastrectomy without evidence of any ulceration.

In February 1954, the patient was admitted to the Hospital for Joint Diseases with a history of several episodes of hematuria, frequency, nocturia, weakness, anorexia and weight loss. Physical examination disclosed a questionable left upper quadrant mass. The intravenous urogram showed a large left renal neoplasm. These findings were confirmed by retrograde pyelography. In addition, the patient had a large prostate and several small bladder calculi. Chest X-ray was negative. The patient underwent a left nephrectomy. The pathology report showed a left renal adenocarcinoma. He was discharged in satisfactory condition and has since then been closely followed in the Out-patient department. The most recent chest X-ray (May 1962) was normal. The intravenous urogram showed a normal right urinary tract and bladder. There was no evidence of recurrence.

In May 1956, the patient was readmitted to The Mount Sinai Hospital for the excision of a small mass of the inner angle of the left lower eyelid which had been growing slowly for the past two years. Physical examination disclosed a one centimeter firm, pink-gray, papular mass with hard pearly edges. The mass was excised and the pathology report showed a basal cell epithelioma with all resected edges free of tumor.

The patient was then readmitted to The Mount Sinai Hospital in July 1959 with a history of prostatism of about seven years' duration. Rectal examination disclosed an enlarged, firm, smooth prostate. The patient responded well to conservative therapy and was discharged with minimal symptoms. He was admitted again in April 1961 with severe and progressive prostatism. Rectally his prostate felt symmetrically enlarged and firm. The intravenous urogram showed a normal right kidney and ureter; the bladder was elevated and contained a calculus. Chest X-ray was negative, barium enema was normal, the gastrointestinal series showed a normal status postsubtotal gastrectomy and gastroenterostomy. All laboratory data were normal including an alkaline and acid phosphatase which were 8.0 and 1.7 King Armstrong Units respectively. On April 28, 1961, the patient underwent a suprapubic prostatectomy and bilateral vas ligation. The bladder contained one small calculus, which was

removed. The pathology report showed fibroadenomatous prostatic tissue. The patient had an uneventful postoperative course and was discharged for further follow-up in the Out-patient department.

The patient was seen regularly in the Out-patient department and was completely asymptomatic for approximately one year. At that time he returned to the Genitourinary clinic (April 1962) complaining of gross total painless hematuria lasting one week. He was readmitted to the hospital. Rectal examination disclosed a stony, hard irregularly enlarged prostate with extension of the induration along the seminal vesicles, more accentuated on the right side. A prostatic perineal biopsy revealed an infiltrating adenocarcinoma of the prostate. Laboratory data were all within normal limits including repeated determinations of the alkaline and acid phosphatases.

Because of the patient's advanced age and the obvious extensive infiltration of the seminal vesicles felt on rectal examination, a radical prostatectomy was not indicated. Therefore it was decided to place the patient on estrogen therapy. In addition, a bilateral orchidectomy was performed and the patient was discharged after an uneventful postoperative course.

In May 1962, the patient was readmitted for a minor viral infection. He gave a history of low grade fever and abdominal pain. All his symptoms disappeared within forty-eight hours. On this occasion the patient was again thoroughly investigated. The laboratory data were all within normal limits including the alkaline and acid phosphatases. Chest X-ray was normal. Intravenous urogram and cystogram showed a normal right kidney, ureter and bladder. A bone survey showed sclerosis and some compression of the sixth thoracic vertebra and some sclerosis of the ninth thoracic vertebra. These changes could be interpreted as metastatic disease but there was no clinical or chemical indication of metastatic spread.

Most interesting were the physical findings of the prostate as felt on digital rectal examination. The prostate felt much less indurated, the induration along the left seminal vesicle has disappeared and there is little residual induration along the right seminal vesicle.

The patient is seen regularly in the Genitourinary clinic. He is completely asymptomatic. The pertinent laboratory data are all normal. He continues on estrogen therapy, taking 24 mg of Chlortrianisen® daily.

DISCUSSION

As noted in the preceding case report our patient underwent multiple surgical procedures for adenocarcinoma of the stomach, adenocarcinoma of the left kidney, basal cell carcinoma of the left eyelid and finally a diagnostic, and then palliative procedure for an extensively infiltrating extracapsular prostatic adenocarcinoma.

Arbitrarily considering a five-year survival rate without evidence of recurrence as a successful result, we may conclude that this patient has been satisfactorily treated by surgical means for three of his four carcinomas. It is now

twenty-two years after the subtotal gastrectomy for adenocarcinoma of the stomach, eight years after left nephrectomy for left renal adenocarcinoma, and six years after excision of a basal cell epithelioma of the left eyelid. By all accepted diagnostic means available today, a recurrence or metastatic spread of any of the three above-mentioned carcinomas has been ruled out.

The most recent carcinoma, in chronological appearance was the prostatic adenocarcinoma. It is of extreme importance and interest to emphasize here again that this neoplasm appeared only one year after a suprapubic prostatectomy* for benign prostatic hypertrophy. From the case history, it can be easily seen that, at that time, all the available diagnostic criteria (such as rectal, digital examination, acid phosphatase and bone survey) pointed to a benign disease and this was later confirmed by the pathological report of fibroadenomatous prostatic tissue.

During the year following the suprapubic prostatectomy the patient had an extensive invasive adenocarcinoma, which by rectal examination appeared to have invaded the seminal vesicles. Because of the obvious inoperability of the lesion and the patient's advanced age, palliative therapy, in this case, estrogens and orchidectomy were the treatment of choice. So far the patient responded satisfactorily to the treatment and we hope that the neoplastic process has been arrested.

This case of quadruple primary carcinomas originating in four different organs conforms to the criteria set forth above. In the table adapted by Werthamer *et al* (1) from Goldstein and Rubin (3), are included two cases which do not conform to the previously mentioned criteria (Goetze and Maddock and associates) because two of the neoplasms originating in the same organ system should have been excluded. For the same reason many other quadruple malignancies reported in the literature were not included in our table.

Multiple neoplasms arising in the same organ system, *e.g.* multiple basal cells carcinomata of the skin, papillomatosis of the bladder, multiple papillary carcinomata of the bladder, polyposis of the colon could lead to the hypothesis of a constitutional, inherent predisposition of this certain organ system to undergo malignant degeneration. Multiple malignant neoplasms in different organs may have a completely different meaning. The fact that our patient survived three carcinomas makes one think that perhaps a cured tumor results in some immunity to other cancers.

A review of the literature (Werthamer *et al* (1), Goldstein and Rubin (3), Warren and Gates (2) and others (4–8)) shows that the incidence of multiple malignancies varies from 0.2 to 7.8 per cent with an average of 2.14 per cent. This percentage will certainly increase due to the greater life expectancy today and the improved diagnostic facilities. The fact that the patient had three previous carcinomas and a suprapubic prostatectomy only one year before his fourth

* All the prostatectomies except the radical perineal or retropubic prostatectomy consist simply in the enucleation of the adenoma, leaving the prostatic capsule in place. A carcinoma may develop in the prostatic tissue of the capsule.

TABLE I*

Multiple Primary Malignancies

Author and year	Age	Sex	Lesion and organ
Goetze, 1913	75	M	1. Adenocarcinoma of stomach 2. Prostate 3. Four carcinomata of descending colon and sigmoid (polyposis of intestine) 4. Carcinoma simplex of rectum
Lauda, 1925	54	M	1. Epithelial carcinoma of tonsil 2. Epithelial carcinoma of esophagus 3. Carcinoma of bile duct 4. Adenocarcinoma of rectum
Luchsinger, 1930	89	M	1. Carcinoma of forehead 2. Carcinoma of bronchus 3. Hypernephroma of kidney 4. Osteochondroma of lung
Goldman, 1945[5]	60	F	1. Medullary carcinoma of left breast 2. Postradiation of carcinoma of chest wall with recurrence 3. Transitional-cell carcinoma of cervix 4. Papillary carcinoma of rectum
Holland, 1945[6]	55	F	1. Adenocarcinoma of breast 2. Carcinoma of thoracic esophagus 3. Basal-cell carcinoma of left cheek 4. Annular carcinoma of transverse colon
Massachusetts General Hospital	78	M	1. Colloid carcinoma of gallbladder 2. Epidermoid carcinoma of bladder 3. Adenocarcinoma of rectum 4. Adenocarcinoma of prostate
Goldstein and Rubin, 1948[3]	54	M	1. Papillary carcinoma of bladder 2. Hypernephroma of right kidney 3. Basal-cell carcinoma of skin 4. Adenocarcinoma of sigmoid
Duncan and associates, 1950[4]	74	F	1. Epidermoid carcinoma labium majora 2. Papillary adenocarcinoma of rectum 3. Adenocarcinoma of fundus uteri 4. Basal-cell carcinoma of buttocks
Maddock and associates, 1956[7]	65	F	1. Undifferentiated carcinoma right breast 2. Papillary cystadenoma with malignant degeneration of right ovary 3. Adenocarcinoma of sigmoid 4. Adenocarcinoma of left breast

* Table adapted by Werthamer *et al* (1) from Goldstein and Rubin (3).

carcinoma developed did not prevent us from strongly suspecting the possibility of a new primary malignant neoplasm. The clinician today should be aware of the possibility of multiple primary neoplasms originating in different organs.

SUMMARY

The subject of multiple primary malignancies has been reviewed together with the criteria for qualification into this category. Another case of four primary neoplasms has been added to the literature.

The condition, although rare now, will become increasingly more common and the clinician should be aware of it.

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The Poison Control Program at The Mount Sinai Hospital

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At the urging of the American Academy of Pediatrics and under the sponsorship of the Department of Health, a Poison Control Program was established in the City of New York in 1955 (1). In addition to a Poison Control Center at the Department of Health, each hospital in the city was requested to institute a poison control plan and to designate a poison control officer. The individual hospital was to establish standardized procedures for emergency therapy of poisonings, plan a program of house staff orientation, and institute a reporting system. The hospital poison control officer was to act as a coordinator and maintain liaison with the Poison Control Center.

The Mount Sinai Hospital of New York City is a 1000 bed institution serving both a large clinic population residing in the surrounding area of East Harlem and a middle and upper income population referred by private physicians practicing primarily in upper Manhattan. No ambulance service is provided.

This report of the poison control activities provides a summary of the poisonings treated at The Mount Sinai Hospital during the first seven years of the program.

METHODS

Each year in July, the purposes of the poison control program are explained to the incoming house staff, and the facilities which are available to them for diagnosis and therapy of poisoning episodes are described.

The emergency room program is under the immediate supervision of the graduate nurses in that area. A tray with emergency drugs and materials for lavage is available. A looseleaf book containing current directives and advice from the Department of Health concerning the therapy for specific poisonings is always at hand. This book is an up-to-date poisoning "encyclopedia." In addition, the following textbooks are available in the emergency room:

1. *Clinical Toxicology of Commercial Products* by Gleason, M. N., Gosselin, R. E., and Hodge, M. C., The Williams and Wilkins Company, Baltimore, Maryland, 1957.
2. *Poisoning* by von Oettingen, W. E.; Paul B. Hoeber Inc., New York, New York, 1954.
3. *Accidental Poisoning in Childhood* by E. Press, American Academy of Pediatrics, Charles C. Thomas, Publisher, Springfield, Illinois, 1956.
4. *Modern Drug Encyclopedia*, Edited by E. P. Jordan; Drug Publications, Inc., New York, New York, 1958.
5. *Physicians' Desk Reference:* Medical Economics, Inc., Oradell, New Jersey.

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When a patient who has ingested a toxic substance is admitted to the emergency room, the physician has access to a 24 hour information service at the Poison Control Center in addition to the foregoing volumes. A telephone call to the Center will usually yield information about the toxic constituents of any commercial product, the signs and symptoms which may be produced by its ingredients, and the most aeceptable current therapy.

When a patient is either discharged from the emergency room or admitted to the Hospital, a special post card (395V) containing preliminary information is sent directly to the Poison Control Center. A more detailed form (45VX) is then completed and sent to the Hospital poison control offieer who evaluates the case, institutes follow-up on in-patients as necessary, and forwards the detailed information to the Poison Control Center.

Personnel of the Board of Health frequently make follow-up visits on poisonings of epidemiologie significance such as that due to lead, corrosives, pesticides,

TABLE I

Summary of Poison Episodes According to Etiology and Age of Patient

	Total	Accident	Suicide	Industrial	Unknown
Under 1 Year	8	8	0	0	0
1–5 Years	165	165	0	0	0
5–10 Years	18	17	0	0	1
10–15 Years	7	5	2	0	0
Over 15 Years	95	42	36	1	16
Unrecorded Age	6	3	0	0	3
Totals	299	240	38	1	20

turpentine, and kerosene, as well as on suicide attempts in the younger age groups.

RESULTS

A total of 299 poisonings were reported to the Poison Control Officer at The Mount Sinai Hospital during the seven year period from May, 1955 through April, 1962. Included are all episodes of ingestion of a toxic substance or a therapeutie product in potentially toxic amounts regardless of the presence or absence of symptoms. Reports were filed by emergency room personnel or, in the case of private patients, by the private physician. A small number of poisonings involving private patients presumably were not reported by the physieian involved so that the statisties reported represent minimal figures for poisonings encountered at this institution. In a few instances, complete information was not given and these data are classified as "Unknown." The episodes have been analyzed according to age, sex, seasonal incidence, cause of the poisoning, type of poison, disposition, and fatalities.

Age: Table I presents data concerning the age distribution of individuals poisoned. One hundred ninety-eight patients (66%) were children less than 15 years old; 95 patients (32%) were over 15 years of age.

In 2%, the age was not recorded. Over half (58%) of all poisonings occurred in children under age five. There were eight episodes reported in children under one year of age. The youngest reported cases were two infants three months of age. One was fed a pesticide; the other was fed a cleaning material, both accidentally.

Sex: There were 123 males, 163 females, and in thirteen cases, the sex was not recorded.

Incidence: The number of poisonings reported during a twelve month period ranged from 24 in 1960 to 63 in 1956. An average of 43 episodes of poisoning occurred each year. A tabulation of poisonings according to the month in which they occurred suggests an increased number during the winter months.

TABLE II

Toxic Agent Involved in Poison Episodes

	Under 1 Yr.	1–5 Yrs.	5–10 Yrs.	10–15 Yrs.	Over 15 Yrs.	Unrecorded Age	Totals
Salicylates	1	46	1	1	10	1	60
Sedatives*	0	9	4	1	31	1	46
Other Medications	2	40	4	3	12	1	62
Cleaning Materials	2	27	2	2	14	0	47
Hydrocarbons and Volatile Agents	1	9	3	0	8	0	21
Pesticides	1	5	1	0	7	1	15
Corrosives	0	7	2	0	3	0	12
Lead	0	10	1	0	0	0	11
Miscellaneous	1	11	0	0	7	0	19
Unknown	0	1	0	0	3	2	6

* Includes: Narcotics and Tranquilizers.

Etiology: Table I also presents the etiologic factors of the poisonings as related to the various age groups. Two hundred forty (80%) of the poisoning episodes were accidental in nature. Thirty-eight were suicide attempts. In twenty the reason for the poisoning was unknown. One industrial poisoning was reported, a thirty-eight year old male cleaner who inhaled carbon tetrachloride.

It may be seen from this table that all the poisonings in children under ten years of age were accidental. Suicide attempts accounted for more than one third of the adult patients treated for poisoning. There were two adolescent patients who also attempted suicide; both were thirteen year old girls.

Type of Poison: The toxic agents involved in each episode are tabulated in Table II. In Figure I, the categories of toxic agents most frequently involved are graphically presented by age group. Salicylates and sedatives (including narcotics and tranquilizers) are listed separately. All other medications are tabulated together. Accidental ingestion of isopropyl alcohol is included in the group of "Other Medications" because of its common use as an adjunct in the therapy of fever.

Medications were involved in 56 per cent of all poisoning episodes (168 cases). Salicylates headed the list and were reported in sixty cases (20%); more than half involved children one to four years of age. There were no reported fatalities due to salicylate poisoning.

Forty-six patients (15%) ingested sedatives, narcotics, or tranquilizers. Almost all of these patients were over fifteen years of age, and most were attempts to commit suicide. Other medications, including many prescription items, were reported in 62 cases (21%).

Most of the patients poisoned by cleaning materials were one to four years of age. Twenty-one patients were poisoned by hydrocarbons or other volatile

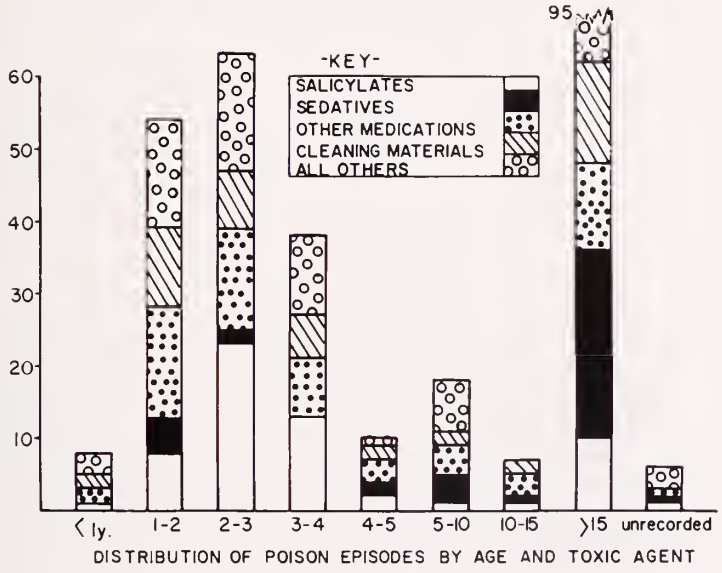

FIG. 1.

agents. Swallowing of corrosive material occurred in twelve patients and ingestion of pesticides in fifteen. Of the eleven patients with lead poisoning, all were under age five except one. The miscellaneous substances involved in nineteen episodes include ink, hair dye, nail polish remover, matches, paint, liquid soap, and spoiled food. Two children ingested expensive perfume, and one child was hospitalized following aspiration of talcum powder. In six episodes, the nature of the poisonous substance was unknown.

Disposition: There were 109 patients (36%) who were poisoned seriously enough to warrant hospitalization; the remaining 190 (64%) were treated as out-patients.

Fatalities: There were 11 fatalities among the 299 patients. The overall fatality rate was 3.7 per cent.

There were two deaths among the children under fifteen years of age; a fatality rate of one per cent. However, of the 66 children who were poisoned

severely enough to require hospitalization, two died (3%). The first was a one year old female with asthma who had been treated with large doses of rectal aminophylline for 48 hours prior to admission. The child became comatose, developed high fever, hematemesis, and convulsions. She died on the day following hospital admission despite therapy. The second child was a 2½ year old female with severe lead poisoning. She died on the fourth hospital day despite treatment with intravenous versene and urea.

There were nine deaths among adult patients; a fatality rate of 10 per cent. Of the 42 adults who were poisoned severely enough to require hospitalization, nine had a fatal outcome (21%). Four of these were adult females who committed suicide; one utilized tranquilizers, and three took barbiturates. These last three had all been under psychiatric care in the past, and one had previously attempted suicide with barbiturates.

In two episodes, adult males developed acute renal failure and died following the accidental ingestion of carbon tetrachloride. Three adult patients died shortly after hospital admission following episodes of chest or abdominal pain, blindness, and coma. The clinical diagnosis of acute methyl alcohol poisoning was confirmed on postmortem examination in all three.

DISCUSSION

Although patients who have ingested poisons represent a small percentage of all cases treated in an active emergency room, the diagnosis and treatment of these patients constitute an important problem in a large voluntary hospital.

As might be expected, children under five years of age are most susceptible. Of special interest is the fact that eight children under one year of age, not yet toddlers, accidently ingested poisonous substances. Medications of all types, cleaning materials, and pesticides were prominent on the list of ingested materials. This suggests that kitchens and bathrooms are especially dangerous areas in which to leave children unattended. The apparent increased incidence of poisonings during the winter months when children are more frequently indoors emphasizes the necessity for closer supervision in the home.

Although poisonings occur more frequently in children, fortunately the fatality rate is lower. This suggests that children may ingest relatively less of a toxic agent or that they are brought to the emergency room and treated more promptly.

A sizable proportion of the adult toxicities were attempts to commit suicide. The availability of all types of medicinals and the increased production of new industrial agents compounds this problem. Of interest are the two suicide attempts by adolescent patients. This problem is being reported with increasing frequency (2).

In addition to tabulating the experience of one institution, this report emphasizes the advantages of a hospital poison control program associated with a central clearing house maintained by the City. Much information has been exchanged with other institutions through this central agency. The emergency room personnel and facilities are available immediately for removal of a toxic substance by either lavage or forced emesis. The physician has immediate ac-

cess, either in the emergency room itself or at the central clearing house, to the latest information about the toxic properties of a preparation, emergency antidotes, and supportive therapy. The poison control officer is on call for consultation and other aid. The attending physicians, house staff, and nursing personnel have developed great enthusiasm, interest, and knowledge in the handling of poison episodes, to the immeasurable benefit of the patient. Numerous incidents recorded in the hospital records would attest the fact that emergency treatment literally saved lives.

Thus far in the modest setup of one hospital, information of sufficient importance to merit more formal dissemination has been acquired in six instances (3–8). It should be emphasized that statistical reports of poisonings from various institutions may not be comparable because of differences in the type of hospital and dissimilarities in the type of the population included (9–10).

Much has been accomplished in the first seven years of this program. There is need for much more to be done in the coming years as an increased number of commercial products and drugs become available. A program such as this, with the immediate availability and dissemination of information on such substances and their toxic potential will aid in the prevention and the treatment of poisonings.

SUMMARY

1. An outline of the poison control activities at The Mount Sinai Hospital and a summary of seven years' experience with this program are presented. A total of 299 poisonings were reported to the poison control officer during this period.
2. Over half (58%) of all poisonings occurred in children under five years of age; 66 per cent of all poisonings occurred in children under 15 years of age.
3. More than one third of poisonings in adult patients were suicide attempts. Two suicide attempts among adolescent patients are reported.
4. The overall fatality rate was 3.7 per cent. Fatalities were caused by aminophylline, lead, barbiturates, a tranquilizer, carbon tetrachloride ingestion, and acute methyl alcohol poisoning.
5. A variety of medications were involved in the poisoning episodes. Emphasis is placed upon the necessity of keeping these products from small children.

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Unusual Wound Complication Following Cholecystectomy for Typhoid Gallbladder

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Although more than five hundred cases of cholecystectomy for gallbladder typhoid carriers have been published during the last 54 years, only a few instances of postoperative typhoid wound infection have been recorded. Since the incidence of typhoid fever has decreased markedly, especially in the United States, such reports have become increasingly rare. Undoubtedly there are still some typhoid carriers around, who harbor bacilli from either an overt or a subclinical attack of typhoid fever which may have occurred many years before. Since most carriers have diseased gallbladders, many ultimately come to surgery and therefore develop a peculiar form of wound infection postoperatively. Such a case is presented, with a review of the pertinent literature.

CASE REPORT

J.J., #197781, a 65 year old Rumanian-born white female was first admitted to MSH on July 3, 1962. She had a forty year history of occasional post-prandial right upper quadrant abdominal pain and mild fatty food intolerance. About ten months prior to admission, the patient experienced chills and fever to 104 degrees F. Her illness was finally diagnosed as typhoid fever by positive blood and stool cultures. Febrile agglutinins revealed typhoid H positive 1-3, 200; and O positive 1-1, 600. She was treated with one gram of chloramphenicol daily for approximately two weeks, after which she became asymptomatic. The patient was readmitted one month later, however, because of intermittent fever. Although blood and stool cultures were negative, she received chloramphenicol for three weeks. Seven months after her initial episode, right upper quadrant abdominal pain and recurrent fever developed. Stool and biliary discharge were both positive at this time for Salmonella typhosa. A diagnosis of acute cholecystitis exacerbating chronic cholecystitis caused by typhoid fever was made. She was admitted for a cholecystectomy.

Physical examination revealed an obese well-developed white female. Blood pressure was 188/75, pulse rate 88, and regular, respiratory rate was 20, and temperature was 100.2°. The abdomen was obese, soft, and non-tender; there were no masses or palpable organs. On the third hospital day, a cholecystectomy was performed under general anesthesia through an upper abdominal paramidline incision. The gallbladder was found to be chronically inflamed, thick walled, and contained several faceted yellow calculi. Dissection was performed from above downwards. The cystic artery and duct were ligated separately with #0 chromic catgut. The gallbladder was removed intact, care being taken in view of the typhoid history, to prevent spillage of bile. Two penrose drains were placed to

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Morrison's pouch, the liver bed was closed over with fine catgut, and the wound repaired with buried wire sutures of 30 gauge steel wire and interrupted silk for the skin. All subcutaneous bleeding vessels were tied off with catgut.

Cultures of the interior of the gallbladder revealed Salmonella typhosa. The pathology report was chronic cholecystitis and cholelithiasis. The nasogastric tube was removed on the first postoperative day and the first wound drain was removed on the second postoperative day. Her course was benign until the fifth postoperative day when her temperature rose to 101.4, and redness was noted surrounding each skin suture. A yellow purulent exudate was seen at the skin edges. The second drain was removed at about this time. Culture of the wound, reported a few days later, revealed Staphylococcus aureus, coagulase positive, and Salmonella typhosa. The sutures were removed on the seventh postoperative day. She was discharged on the following day. There was a small amount of purulent exudate at the drain site. The patient received no antibiotics at any time during her hospitalization. She was seen at an office visit four days later at which time it was noted that there was considerable discharge of reddish-brown fluid from the original drain area. There were tiny abscesses at the point of each skin suture site. Hot, wet dressings were prescribed.

The patient was readmitted to The Mount Sinai Hospital four days later. The temperature was 101° and the drainage area and each suture site discharged a small amount of yellow-green fluid. There was pain and tenderness over the right lower chest and subcostal region. Treatment with chloramphenicol was instituted and continued for six days with reduction in the fever and change in the character of the drainage to a thick red-brown material. The suture abscesses healed quickly. Cultures on admission showed the same organisms as previously. The drainage slowly lessened, symptoms abated, and the patient was discharged on the 17th hospital day. When next seen, five weeks later, the wound was well healed and the patient was asymptomatic. She has remained well.

COMMENT

It was found in the early 1900's that many typhoid and paratyphoid patients continued to discharge bacilli in their feces following recovery. The incidence ranged from 0.5 to 11.6 per cent. Obviously, these carriers constituted a serious public health problem. Dehler demonstrated in 1907 that the typhoid carrier state could be terminated by cholecystectomy (1). The typhoid bacilli may persist for years in four areas of the human body: the urinary tract, intestinal mucosa or Peyer's patches, biliary radicles of the liver, and gallbladder. About 75 to 80 per cent of these are lodged in the gallbladder. Failure to cure the carrier by cholecystectomy is commonly due to foci in one of the other areas.

Eichoff collected from the German literature up to 1930, 102 cases of typhoid carriers treated by cholecystectomy with an 81 per cent cure rate (2). In the last thirty years, 400 additional cases have been reported with cure rates ranging between 68 and 100 per cent (3). Although positive cultures were obtained in the vast majority of these gallbladders, only a few examples of postoperative

typhoid wound infection were reported. Scant attention is paid to the condition of the postoperative wound in most of the articles on the subject. The New York City Health Department has never indicated any special precautions

TABLE I

Author	Appearance of Gallbladder	Appearance of Postop. Wound	Etiological Organism	Duration of Infection
1 Altemeier (5) 1945	Gallbladder dilated to 5 times normal size with thick, brown bile	Abdominal wall abscess	S. typhosa	Not stated
2 Steiner (6) (case 3) 1950	Empyema of gallbladder with perieholecystitis and eholelithiasis	Profuse secretions from drainage tract	S. typhosa	Less than 3 years
3 Steiner (6) (case 4) 1950	Phlegmonous cholecystitis, cholelithiasis and right subphrenic abscess	Abdominal wall abscess	S. typhosa	6 months
4 Steiner (6) (case 5) 1950	Phlegmonous cholecystitis with walled off perforation, cholelithiasis	Abdominal wall abscess	S. paratyphi B.	Not stated
5 Steiner (6) (case 7) 1950	Moderate cholecystitis and cholelithiasis	Wound fistula	S. paratyphi B.	More than 3 months
6 Langenskiöld (7) 1953	Single bean-sized calculus	Normal until 6 months postop. when subcutaneous swelling appeared	S. paratyphi B.	$3\frac{1}{2}$ years
7 Current case 1962	Chronic cholecystitis and cholelithiasis	Erythema around sutures on 5th day followed by suture sinus abseesses and red-brown profuse drainage	S. typhosa	Less than 9 weeks

for the care of these patients undergoing cholecystectomy. However, their rules are very specific for those patients with positive stool and duodenal cultures. These include continued contact with the authorities and refraining from food handling.

Harkins states in his recent textbook: "Wound infections may also be caused by the typhoid bacillus, particularly after cholecystectomy for the removal of the gallbladder in a carrier patient" (4). Yet six cases only could be culled from the literature (see table). He refers the reader to a case, presented by Altemeier, in which the patient some months postoperatively was found to have a tender, firm, right upper quadrant mass which was incised and drained (5). The abscess cavity was filled with thick, grey pus and was lined by a thin grey sac. The wound healed following drainage with applications of tyrothricin ointment.

Steiner presented seven cases of unsuspected typhoid infection of the gallbladder out of 354 cholecystectomies for chronic cholecystitis (6). In four of these seven, abscesses or draining fistulae developed from which typhoid bacilli were cultured. None of these patients gave a history of a clinical attack of typhoid fever.

Langenskiöld published the case of a known carrier whose abdominal wall was not protected during cholecystectomy (7). The gallbladder was emptied by puncture before removal. Nonabsorbable (silk) sutures were applied to the peritoneal edges and were used to close the anterior rectus sheath. Six months later, a tender mass appeared lateral to the scar which subsequently opened and drained several times, occasionally discharging silk sutures. It was not until three years later, after an extensive revision and treatment with chloramphenicol, that the wound healed completely.

Several observations can be made from these cases. Of primary importance is a carefully taken history with an attempt to elicit an episode of typhoid or paratyphoid fever. Unfortunately, the attack is sometimes subclinical which may, nevertheless, create a carrier state. When a history of an attack is obtained, the surgeon is alerted to take precautions. Packing off the operative field during dissection of the liver bed and prevention of leakage from the cystic duct at the time of transection are important technical points.

The contents of the gallbladder should be cultured following removal. The finding of specific organism infection calls for appropriate antibiotic therapy. It is advisable not to use nonabsorbable suture material during closure of the abdominal wound because of the possibility of contamination. Finally, the question of prophylactic antibiotic therapy arises. Since chloramphenicol has been demonstrated to be highly effective against salmonella both *in vivo* and *in vitro*, it would appear to be advisable to use it postoperatively in a typhoid carrier.

CONCLUSIONS

A case is presented of Salmonella typhosa wound infection following cholecystectomy for chronic cholecystitis in a typhoid carrier. Several similar cases reported in the literature are reviewed. It is suggested that, to avoid such infections, the following precautions be taken:

1) Careful history taken to elicit prior episode of typhoid fever.
2) Routine culture of gallbladder contents after excision.

3) Avoidance of nonabsorbable suture material.
4) Chloramphenicol coverage following cholecystectomy.

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Response of Advanced Breast Carcinoma to the Combination of the Antimetabolite, Methotrexate, and the Alkylating Agent, Thio-TEPA

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INTRODUCTION

The role of cytotoxic agents in medical and postsurgical management of breast carcinoma has recently been under critical re-evaluation as a result of Moore's widely publicized advocacy of thio-phosphoramide (thio-TEPA) for routine intraoperative and postoperative chemotherapy (1–3). The tumor-inhibitory action and relative clinical safety of thio-TEPA alone was first demonstrated by Bateman and colleagues in 1955–1956 (4). Her favorable palliative findings were not promptly confirmed by other investigators due to troublesome variation in the stability and potency of the initial supplies of thio-TEPA, as well as differences in dosage schedules and duration of drug administration. A relatively high incidence of objective remission induced by thio-TEPA in patients with advanced breast carcinoma was subsequently confirmed in both European and American studies (5–8). The incidence of response to thio-TEPA was at least equal to the twenty to forty per cent rate of remission resulting from the usual surgical and medical methods of hormonal control. In interpreting the therapeutic effect of thio-TEPA, it should be noted that the cytotoxic action of such alkylating agents as thio-TEPA extends not only to neoplastic cells, but also to gonadal tissue and vaginal cytology (9). Alteration of adrenal function with reduction of 17-Ketosteroid and increase in 17-hydroxysteroid excretion has also been observed after thio-TEPA administration to breast carcinoma patients (10).

The potential clinical value of the folic acid antagonist, Methotrexate, was reported over ten years ago by one of us (E.M.G.) in collaboration with Schoenbach and Colsky (11). Taylor (12) and Wright (13) had likewise noted that an antifol, Aminopterin, exhibited some inhibitory effect on human breast cancer. In Wright's recent summary of her experience, Methotrexate alone was noted to induce ten objective responses among a group of 36 patients (14). Despite these observations, the general impression, as recently reviewed by Zubrod, is that Methotrexate "rarely affects breast cancer" (15). The mechanism of action of antifols extends well beyond direct effects on various types of neoplastic tissues. The profound inhibitory effect of folic acid deprivation on normal gonadal tissues was demonstrated by Hertz in 1949 (16). A marked sex difference in the toxicity of antifols with the better tolerance of females

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eliminated by adrenalectomy was observed by one of us (E.M.G.) in rodents (17). Marked inhibition of steroid excretion during administration of antifols to patients with breast carcinoma was noted by Higgins (18) and others (19, 20) many years ago.

Since the relative safety of thio-TEPA and Methotrexate, individually, as antineoplastic agents has been established, a study was undertaken of the toxicity and therapeutic effects of full simultaneous therapeutic doses of both drugs in advanced breast, ovarian, and other solid neoplasms. It was hoped that clinical synergism might be achieved without significant additive toxicity, as has been observed in experimental rodent tumors treated with combinations of alkylating agents and metabolic inhibitors (21). Our clinical experience with this combination of thio-TEPA and Methotrexate in advanced ovarian carcinoma has already been published (22). Some of the theoretical and practical aspects of the use of the rapidly acting Methotrexate in patients with solid tumors have also been elaborated (23). The mechanism of action of the long-acting thio-TEPA has been discussed in the ample literature on alkylating agents (nitrogen mustards).

Presented below are results of treatment of advanced breast carcinoma in forty patients given thio-TEPA and Methotrexate during the past three and one-half years. This study did not include any recent postoperative cases. Our patients had developed "late" metastatic disease, in almost all cases recurrent after treatment with local radiotherapy, oophorectomy, and either testosterone or estrogens. This series represented an essentially unselected group of patients presenting for chemotherapy of advanced disseminated and often terminal disease. Only patients with a previous history of major gastrointestinal bleeding were rejected for therapy with this combination of cytotoxic agents. Although controlled survival statistics were not derivable from our study, data on the objective response rate and duration of remission were obtained among patients who were no longer responsive to the more usual therapeutic modalities. In addition, the safety of this combination of "toxic" chemotherapeutic agents could be assessed among a variety of risk categories.

MATERIALS AND METHODS

A priming course of parenteral thio-TEPA and a full oral course of Methotrexate to the point of minimal antifol toxicity were administered simultaneously in forty patients with advanced breast carcinoma. Twenty-four of these patients were hospitalized at The Mount Sinai Hospital on private or ward services. The remainder were ambulatory when started on combination therapy. The priming dosage of thio-TEPA, in all patients, consisted of 15 mg per day to a total of 60 mg, intramuscularly or intravenously. The Methotrexate was given orally in doses ranging from 7.5–12.5 mg per day for three to nine days, always until the first symptoms or signs of stomatitis appeared. The Methotrexate was stopped abruptly on the morning when first definite symptoms of an impending stomatitis were observed. The aggregate dose of Methotrexate necessary to induce the antifol effect varied from 0.4 mg to 1.5 mg per

Kg per week. The wide variation in dosage (Chart 1) reflected differing risk categories and evidently the varying endogenous folic acid reserves encountered among these cancer patients. Poor risk patients, given the lower doses, were those with severe weight loss, semistarvation, anemia, fever, recent diuretics or antibiotics, marked cachexia, azotemia, or history of recent extensive radiation therapy.

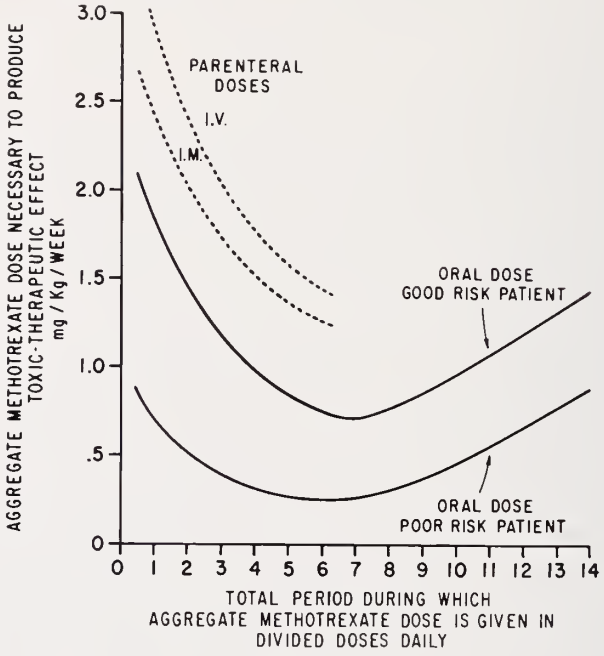


CHART 1

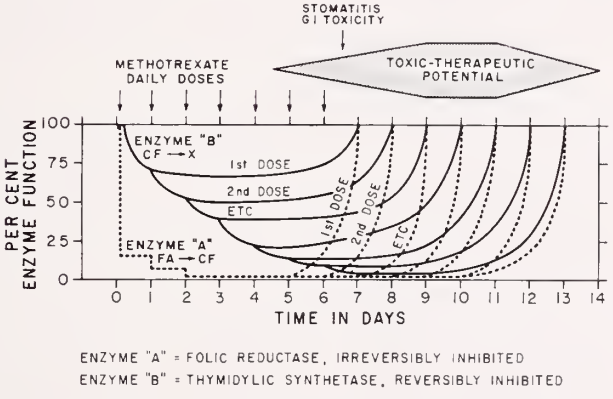
The cumulative delayed anti-enzyme toxic effect of serial Methotrexate doses results in a downward slope in the curves of aggregate tolerated dosage when doses are divided and given daily during the first week of therapy. This scheme demonstrates:

(a) The greater tolerance, i.e., lessened toxicity, of parenteral doses of antifol (due to excretion).
(b) The wide range in tolerated oral dosage between good and poor risk patients.
(c) The more predictable correlation of time-dose-response when antifol dosage is divided daily and given orally over a one week period.

The first bout of antifol stomatitis usually preceded, and was not necessarily accompanied by leukopenia, as noted previously in patients with solid tumors (carcinoma or sarcoma) (23). The dosage schedule was intended to induce the folic acid deficiency state (Chart 2) gradually enough so that the oral and upper gastrointestinal symptoms could signal the need for stopping the drug before any severe depressive effects occurred on the hematopoietic system. The stomatitis first consisted of burning tongue and mouth, followed by the appearance of flat, white atrophic areas of epithelium on buccal mucosa, tongue or lips. The stomatitis and the toxic-deficiency state usually became more intense on the second and third day after withdrawal of medication. Improvement usually followed rapidly with full recovery in five to seven days (Chart 2).

Anorexia often accompanied the clinical antifol effect, and, in some instances, was associated with nausea, crampy abdominal pain, vomiting, diarrhea, low-grade fever, and rash, in order of decreasing frequency (See table). Mild, incomplete alopecia was a late antifol effect in some patients. Mild to moderate nausea or vomiting was the principal side effect of the first week of thio-TEPA therapy. This usually responded to anti-emetics.

Maintenance thio-TEPA therapy was started in the third or fourth week after the initial combination treatment at a dose of 15 mg intramuscularly, once per week. The maintenance thio-TEPA dosage was aimed at producing a constant mild leukopenia between 3,500 to 5,000 white blood cells per cu mm. After several months, it was sufficient to give the thio-TEPA once every two or three



ENZYME "A" = FOLIC REDUCTASE, IRREVERSIBLY INHIBITED
ENZYME "B" = THYMIDYLIC SYNTHETASE, REVERSIBLY INHIBITED

CHART 2

The time-dose relationship of Methotrexate therapeutic effect vs. its rapid anti-enzyme action is shown schematically as antifol is given to patients in daily oral doses. The inhibitory antifol action is exerted on two sets of related enzymes, generically designated as "folic reductases" and "thymidylic synthetases." Recovery in these enzymes usually occurs about one week after the patient has received any dose or series of doses of antifol. The maximum therapeutic effect occurs three to four days after stopping the drug.

weeks to maintain this minimal continuing leukopenia. The second course of Methotrexate was given three to five weeks after initiating the original combination chemotherapy and while the patient was kept on maintenance thio-TEPA. Conclusions regarding the full efficacy of the chemotherapy were held in abeyance for two months, i.e., until the patient had received two courses of Methotrexate, together with the necessary amount of thio-TEPA to produce a modest leukopenia over a four to six week period.

Maintenance thio-TEPA was continued indefinitely in all those who had responded, until the first evidences of recurrence were observed. A third course of Methotrexate was given at the first sign of recurrence or six months after initiating the chemotherapy. If no response was obtained in recurrent disease, the patient was designated as "combination resistant." A course of Cytoxan, 5-Fluorouracil, or Vinblastine, was then given to these resistant cases which were usually entering a terminal state.

RESULTS

Responses

In this series of forty patients with advanced metastatic breast carcinoma, there were 25 or 60 per cent who showed rapid objective improvement (Table 1) for two months or more after treatment with the combination of thio-TEPA and Methotrexate. Thirty-four of the forty patients had previously received testosterone therapy and twenty-nine had undergone oophorectomy two months or more prior to presenting with progressive hormone-unresponsive metastatic disease. Ten of the objective responses to combination chemotherapy were classified as excellent, five as good, and ten as fair. Excellent responses consisted of *apparently complete* gross regression of metastases for three months or longer. Good responses were characterized by definite but not complete regression of observable metastatic disease. The clinical remission in thirteen of

TABLE 1

Results: Combination Chemotherapy (TP + MTX) Advanced Breast Carcinoma

Objective Responses		Mos. in Remission	
		>6	>12*
Excellent	10	8	5
Good	5	5	2
Fair	10	2	1
None	11	—	—
Incomplete Rx with Failure	3	—	—
Toxic Death	1	—	—

* Only 10/40 survived >12 mos. in this series

these fifteen cases of good or excellent regression persisted for six months or longer. The "fair" responses persisted for two to three months or longer, and were manifested principally by a clinical and systemic improvement with only slight objective regression in observable metastatic disease. These ten fair responses appeared to represent an arrest of previously progressive disease. Remissions of one year or longer occurred in eight, or twenty per cent of the total series treated. Only ten of forty patients in this series survived more than one year despite all subsequent modalities of therapy. Thus, when progressive disease resistant to the cytotoxic combination developed, almost all patients died within a brief period (1–2 months) despite other therapeutic attempts. The advanced nature of the clinical material was also illustrated by the short survival of the eleven failures after adequate treatment with thio-TEPA and Methotrexate. Only one case in this group of failures survived beyond six months.

Figures 1–16 show objective regression of pulmonary metastases in four patients. Figures 17 to 20 illustrate the regression of a massive fungating, ulcerating tumor involving the entire breast. These responses became apparent

eight to twenty days after starting the combination. In most patients the first signs of regression were noted two to seven days after the onset (Chart 2) of the antifol effect (such as stomatitis), i.e., usually several days before such thio-TEPA induced effects as leukopenia were becoming manifest.

The incidence of regression according to major sites of gross clinical involvement in forty patients is shown in Table 2. The highest incidence of objective regression from combination chemotherapy was seen among eight of ten patients with multiple nodular skin metastases. Many of these lesions had developed within previously irradiated skin portals. The maximum duration of control varied from five to eight months despite the fact that rapid total regression of infiltration had occurred in most of these cases. Soft tissue, lung and pleural metastatic disease regressed in more than half (13/20) of our cases (Table 2) with major metastases in these areas. The excellent results of treatment in five of

TABLE 2

Regression in Major Sites of Clinical Involvement 40 Patients

Skin	8/10
CNS—Brain	5/8*
Soft Tissue	5/8
Lung	4/7
Pleura	4/5
Osseous	3/9†
Generalized	3/5
Hepatic	2/7
Abdominal	2/5

* With radiotherapy.

† None showed accelerated recalcification of osteolytic metastases.

eight cases of intracranial metastases (Table 2) were obtained by employing local radiotherapy to the skull with the simultaneous combination of systemic thio-TEPA and Methotrexate. All these cases of intracranial metastases had some extracranial metastasis which could be observed free of any radiotherapy effect (see figures). Longterm control for more than one year, despite the presence of generalized disease was attained in five patients with demonstrable metastases in the brain, skull, lung, skeletal system, and abdomen. Maintenance thio-TEPA and intermittent Methotrexate therapy have been administered for three and one half years in one such patient and for over two years in two other patients with cerebral and generalized metastases.

The fewest responses were obtained in diffuse osseous disease and in hepatic metastases. Although bone pain and other symptoms of osseous dissemination improved in three of nine cases with predominantly bone lesions, there was no evidence of accelerated recalcification of the osteolytic metastases in the patients who showed the disappearance of bone pain. The worst prognostic situation involved massive hepatic metastases. Regression of metastatic hepatomegaly with longterm palliation (six months or longer) was obtained in only

two of seven cases of disseminated metastases in which metastatic hepatomegaly was the conspicuous clinical feature.

The precise time relationship of the antifol effect to tumor regression was most easily observed in the ten patients with multiple nodular skin metastases. Eight of these ten showed marked resolution or total disappearance of multiple nodular chest wall infiltrations within two or three days after the onset of antifol stomatitis. Some of these skin lesions which had vanished, recurred grossly as early as three to six weeks after regression. Although these recurrences showed less complete response after each subsequent course of the Methotrexate (accompanied by thio-TEPA maintenance therapy), the clinical antifol effect always coincided with the repeated response. A state of complete tumor resistance to the combination of these agents was found within ten

TABLE 3

Toxicity to Combination Chemotherapy (TP + MTX)

Stomatitis	40
Leukopenia	38
Anorexia	34
Nausea	31
Epigastric pain	21
Vomiting	12
Thrombopenia	11
Fever	8
Alopecia	7
Diarrhea	6
Rash	5
Gastrointestinal Bleeding	3
Purpura	3
Induced Hypoplastic Marrow	2
Nasal Bleeding	1
Acute Fatal Shock (Postadrenalectomy)	1

months among this group of eight with highly sensitive tumors. The longest duration of regression of soft tissue metastases is now (at the time of writing) twenty months without recurrence.

In this study, the development of regression after combination chemotherapy showed no relationship to age, premenopausal or postmenopausal state, or previous radiation therapy, oophorectomy or endocrine therapy. It may be noted, however, that there were no remissions greater than six months among our eight patients less than forty-five years of age. Our results thus indicate that more than half the cases of skin, soft tissue, visceral and central nervous system (V. I.) metastases may be expected to regress after combination chemotherapy regardless of their course under previous therapy.

Toxicity and Dosage

All forty patients in this study developed one or more bouts of antifol stomatitis after completion of Methotraxate therapy (Table 3). Mild stomatitis

was reproduced two to four times in most of these cases. Only two patients failed to show a leukopenia despite two courses of Methotrexate to the point of antifol stomatitis while also receiving the thio-TEPA. Although acute anorexia was induced at least once by the drug combination in 34 patients, and nausea occurred in 33, vomiting was produced in only 12 patients. A thrombocyte count below 80,000 cu mm, secondary to the drug combination was observed in eleven patients. Fever at the height of the period of toxic-therapeutic potential (Chart 2) was observed in eight patients, presumably secondary to induced tissue or tumor necrosis. Almost all patients showed some slight, insignificant diffuse thinning of the hair, but a severe antifol-induced alopecia developed in 7 of 32 patients (excluding those receiving radiotherapy to skull). In some of these cases of alopecia, the hair returned at a later date with dark pigmentation, i.e., (grey to black), together with a distinct increase in coarseness, thickness, and curliness of the hair. This recovery from alopecia occurred four to six weeks after the Methotrexate had been stopped. Mild, transient gastrointestinal bleeding, purpura, or nasal bleeding with moderate induced anemia was seen at the height of the thrombopenic thio-TEPA effect in seven patients. The withdrawal of thio-TEPA for three to four weeks was sufficient to allow recovery from the bleeding syndrome. Transient rash of three to five days' duration at the height of the Methotrexate effect was evident in five patients.

Life-impairing toxicity was produced in only three patients (Table 3). Severe pancytopenia developed in two patients, 8 and 11 months respectively, after beginning the drug combination. Three courses of Methotrexate had been given in one case and four courses in the other while on thio-TEPA maintenance. Transfusion was necessary in one case, although both patients recovered within four weeks after withdrawal from chemotherapy. More frequent examinations and closer attention to warning signs could have minimized these severe toxic reactions. The only case in which the drug combination precipitated a death was in an adrenalectomized patient with far advanced diffuse carcinoma involving the skin and subcutaneous tissues of the entire trunk, face and extremities and the lungs. Although she was entering a terminal phase, a shock-like state suddenly developed on the fourth day of combination therapy. In retrospect, an increase in her usual maintenance steroid dosage might have permitted survival for the eight to ten days necessary to exert any therapeutic potential of the combination.

In this study, as in our previous reports (22, 23), it was evident that the antitumor action of Methotrexate could not be obtained without inducing a minimal toxic effect. Not only was there a wide variation in the dosage, necessary to induce the antifol stomatitis, but it was often impossible to predict toxicity. In an attempt to approximate and anticipate the necessary aggregate weekly dosage, patients were placed into good and poor risk categories. Chart 1 illustrates the wide variation of dosage necessary to slowly and safely induce the antifol effect. Of utmost importance was the *immediate* interruption of any additional Methotrexate as soon as the very first signs of oral antifol effects appear, usually five to eight days after starting therapy.

CASE REPORTS

Case 1

R.L. (*MSH #152379*), a seventy-four year old female, refused mastectomy for a slowly enlarging mass in the right breast of one and one-half years' duration. Needle biopsy of the mass, 7 x 10 cm, revealed adenocarcinoma. Chest x-ray showed large pulmonary metastases in both lung fields (Fig. 1). The patient was given a course of oral Methotrexate, 7.5 mg

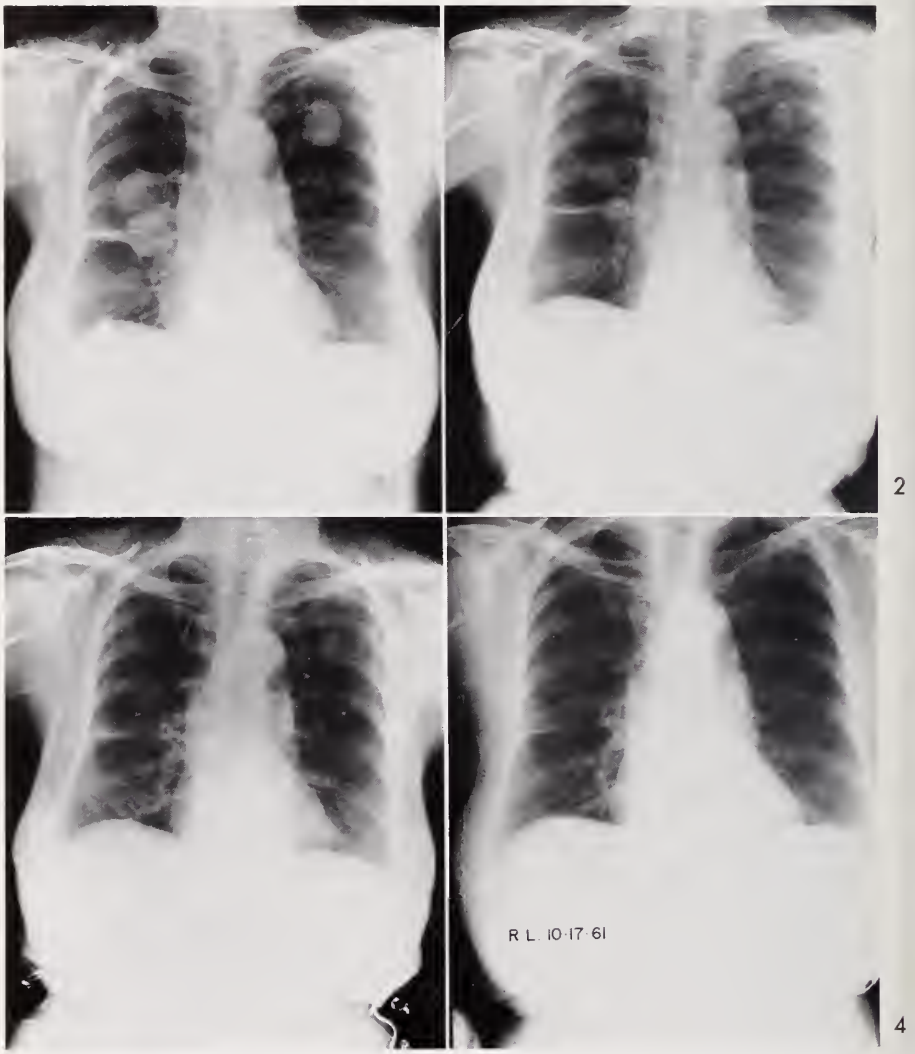


Fig. 1. Pretreatment status of pulmonary metastases in Case #1.

Fig. 2. Regression of pulmonary metastases as seen 6 weeks after starting combination chemotherapy. The patient had just completed the second course of Methotrexate while on thio-TEPA maintenance.

Fig. 3. Further rapid regression of lesion. The large soft tissue tumor mass in the right breast is visibly reduced in size.

Fig. 4. Essentially total disappearance of pulmonary metastases and massive right breast tumor, occurring for 11 months while on combination chemotherapy. For details, see Case summary #1.

per day for nine days, to the point of minimal stomatitis, together with 60 mg of intramuscular thio-TEPA during the first week of Methotrexate therapy. Several days after the onset of the antifol stomatitis, the patient noted marked reduction in the size of the breast mass. Maintenance thio-TEPA was begun four weeks after these priming doses had been given. A second course of Methotrexate was given five weeks after the first course. Chest x-rays taken six weeks and eight weeks after initiating this combination therapy revealed marked reduction in the pulmonary metastases (Figs. 2, 3). The primary lesion in the breast was no longer palpable at this time. The patient was maintained on thio-TEPA, 15 mg, intramuscularly, every two or three weeks for ten months, with exhibition of a moderate steady leukopenia. A third and fourth course of Methotrexate was given six and eight months after the initial combination therapy. After ten months of this combined regimen, anemia and purpura developed in association with depression of white blood cells to 2,800 and platelets to 60,000/cu mm. A single transfusion was given after withdrawal of the thio-TEPA. Recovery of peripheral blood was rapid within three weeks. Chest x-ray one year after initiating the combination chemotherapy showed virtually no evidence (Fig. 4) of the large pulmonary metastases previously seen. The breast lesion, which had regressed completely and remained under control for a year after starting therapy, now began to show progressive regrowth. Due to the development of the hematological depression and purpura while on thio-TEPA and Methotrexate therapy, the patient was begun on testosterone and Cytoxan therapy. The metastatic lesions showed no response after two months on this regimen. Massive estrogen therapy was then instituted but after three months failed to prevent the development of extensive pulmonary metastases. She was then admitted with cerebral metastases in a terminal state. This time, thio-TEPA and Methotrexate were given in combination with steroids and androgens. She made a dramatic transient recovery from an apparently moribund state. She died with progressive cerebral and pulmonary metastases, five weeks after this last four-fold trial of chemotherapy and hormone therapy.

Case 2

Right radical mastectomy for adenocarcinoma was performed on this 34 year old female in 1958. Routine chest roentgen examination showed a "solitary" pulmonary nodule in the right upper lobe adjacent to the lateral chest wall (Fig. 5) in August, 1961. Dr. Herbert C. Maier performed an exploratory thoracotomy and wedge resection of a mass of metastatic adenocarcinoma at Lenox Hill Hospital. On September 28, 1961, a bilateral salpingo-oophorectomy was performed. Persistent cough and right chest pain developed in November, 1962. Roentgen examination (Figs. 6, 7) showed a diffuse hilar nodular infiltration extending towards the periphery of the right upper lobe. Extension of this lesion occurred rapidly (Fig. 8) in association with the development of severe intractable headache. Chemotherapy with thio-TEPA was begun intramuscularly at the dosage of 15 mg every other day for a total of 60 mg. Suddenly, three days after starting this regimen the patient developed a grand mal seizure. Emergency hospitalization was instituted at Park East Hospital. Examination showed moderate papilledema in the right fundus. Anticonvulsant therapy (Dilantin and Phenobarbital) was instituted in conjunction with a course of oral Methotrexate (7.5 mg for 7 days) to the point of stomatitis. The headache and visual symptoms subsided as the antifol stomatitis developed. Within two weeks after the initial course of thio-TEPA and Methotrexate had been concluded, she was started on maintenance thio-TEPA. A second course of Methotrexate was begun four weeks after the first course. The lowest white count during this combined therapy was 4,200 per cu mm, without depression of platelets. Papilledema gradually improved. Chest x-ray showed complete clearance of the pulmonary lesions in January 1963, six weeks (Fig. 9) after the combination of thio-TEPA and Methotrexate had been started. She was then begun on an ambulatory course of maximal cobalt radiotherapy to the skull through upper lateral portals. Four months after the initial development of pulmonary and cerebral metastatic disease, this patient is in clinical and objective remission. She is asymptomatic except for drug and x-ray induced alopecia and mild fatigue and mental depression.

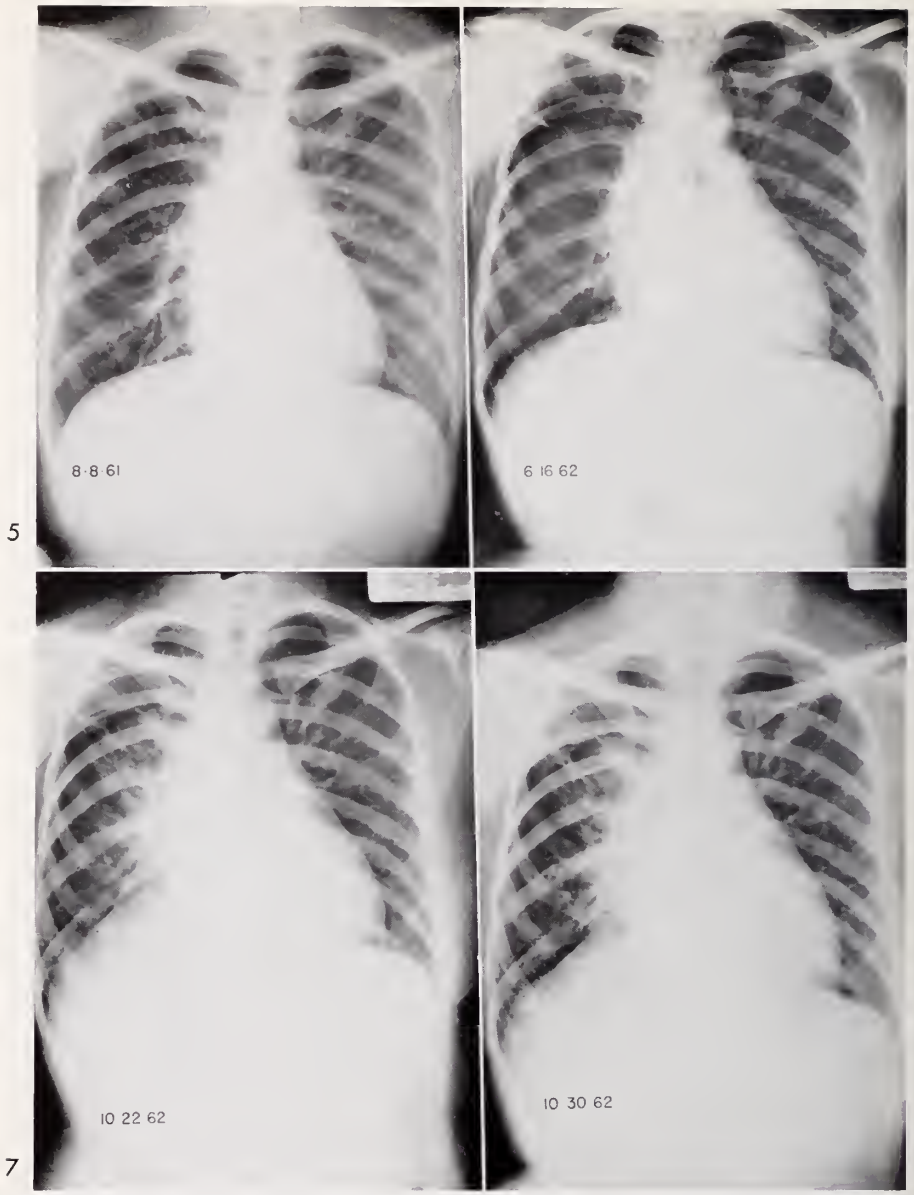


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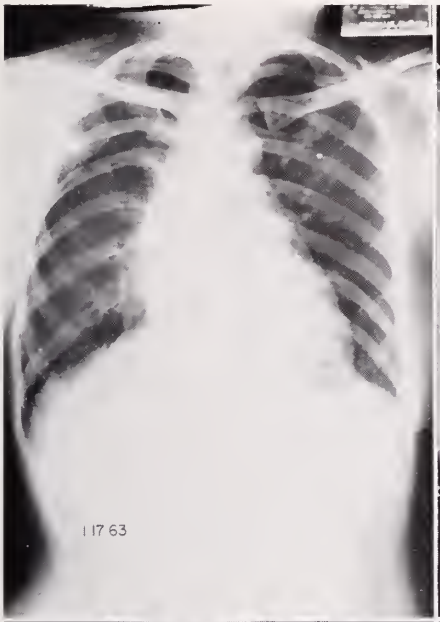
FIG. 5. Pulmonary metastasis in right upper lobe laterally near chest wall (Case #2).
FIG. 6. Status of lungs 9 months after wedge resection of right pulmonary metastasis.
FIG. 7. Neoplastic late recurrence in right lung field.
FIG. 8. Rapid extension of neoplastic infiltrate in right lung field. X-ray taken eight days after Fig. 7.

Case 3

E.L. (154290), a 51 year old female, who underwent a radical mastectomy 1½ years previously, developed weakness in the left hand and arm, weight loss, and cough. A generalized convulsion occurred three weeks prior to hospitalization. On admission, she showed severe cerebral dysfunction, confusion, left hemiparesis, a hemisensory syndrome, and profound

aphasia. A carotid angiogram revealed a mass in the right frontal parietal area, and a stain in the left frontal parietal area, consistent with a second metastatic lesion. During the first two weeks of her hospital stay, she became progressively worse with repeated convulsive episodes, severe headaches, and nausea, development of papilledema, and a marked organic



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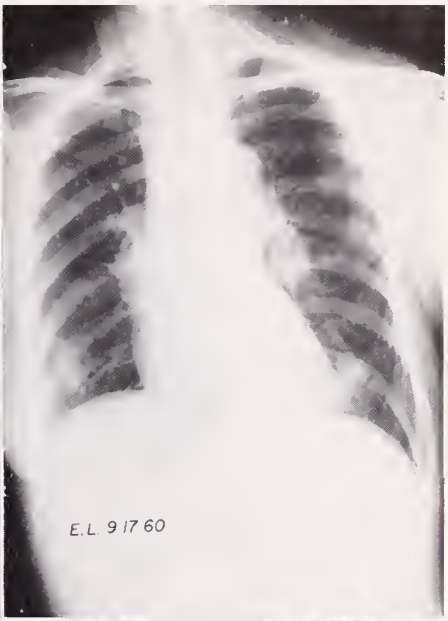

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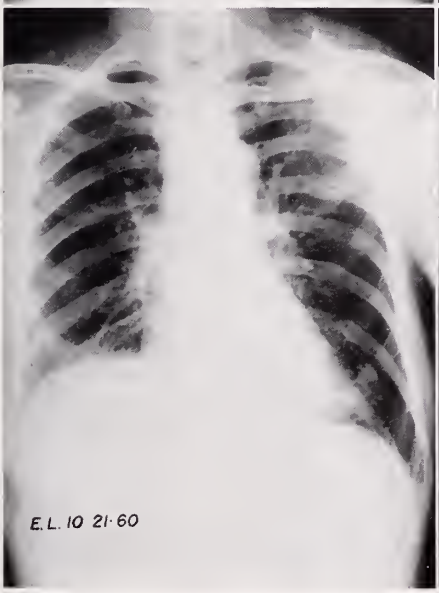

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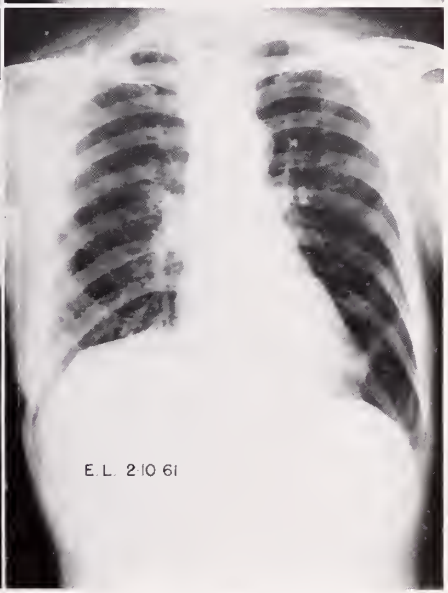

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FIG. 9. Regression of pulmonary infiltrate 6 weeks after therapy with thio-TEPA and Methotrexate. Case #2.

FIG. 10. Bilateral basilateral and left hilus metastases in Case #3.

FIG. 11. Regression of metastases, 5 weeks after initiating combination chemotherapy.

FIG. 12. Regression maintained after 3 months on combination chemotherapy. See Case summary #3 for details of further course.

mental syndrome. X-rays of the chest revealed bilateral metastatic disease (Fig. 10). Electroencephalogram revealed a severely abnormal pattern indicating diffuse cerebral dysfunction, with at least one lesion of a focal nature in the right anterior cerebral region. She was given a course of combination chemotherapy consisting of a priming dose of thio-TEPA and a full course of Methotrexate to the point of toxic stomatitis. Simultaneously, on the basis of the bilateral multiple cerebral metastases, radiation therapy to the skull was administered with broad lateral portals. Nine days after initiating chemotherapy, at the height of the maximal stomatitic antifol effect, the patient began to demonstrate remarkable neurological improvement. Serial chest x-rays revealed regression of the pulmonary metastases (Figs. 11, 12) due to chemotherapy alone. Her neurologic status improved rapidly. She was discharged within three weeks, able to walk, and without an organic mental syndrome. The hemiplegia had disappeared, leaving only a mild residual difference in the extremity reflexes. She was maintained on thio-TEPA for eight months after discharge from the hospital, and was given two courses of Methotrexate to the point of minimal stomatitis in the second and fourth months after discharge from the hospital. Thereafter, she failed to maintain optimum regimen of chemotherapy after eight months of close supervision. Due to inadequate chemotherapy, and/or the natural recurrence of resistant disease, she developed massive pleural effusion and pulmonary metastases one year after discharge from the hospital. No clinical recurrence of the intracranial disease was noted. She was readmitted with acute pulmonary tamponade in a terminal status. Death occurred three days after hospitalization in insufficient time to reinstitute chemotherapy.

Case 4

Three years after mastectomy, this 49 year old female developed bone pain, slight cough, an organic mental syndrome, external ocular palsies, visual field deficits, and unilateral sensory-motor deficit. The neurologic aspects were quite similar to Case #3. X-ray examinations revealed a pulmonary metastasis (Fig. 13), and a thoracic vertebral metastasis. Radiotherapy to the skull was given simultaneously with thio-TEPA and Methotrexate as outlined for Case #3. The neurologic status improved rapidly within 7 to 14 days after initiating combined chemotherapy and radiotherapy. A second course of Methotrexate was given four weeks after the first, and again to the point of minimal stomatitis. The pulmonary lesion disappeared within 4 to 6 weeks (FIG. 14) after initiating chemotherapy. Bone pain at first improved, but recurred within three months, at the site of the thoracic vertebral metastasis. After five months of maintenance thio-TEPA with clinical palliation, the patient developed intractable progression of bone pain. This failed to respond to radiation and testosterone therapy. She showed progressive deterioration, and died, eight months after initiating cytotoxic chemotherapy.

Case 5

J. W. (#141929), a 55 year old female, with bilateral mastectomies for breast carcinoma, developed pain in the left lower extremity early in 1960. In August, 1960, there was evidence of radiculitis involving the lower lumbar, and upper sacral routes on the left side. Myelogram and x-ray examination showed osteolytic involvement of the fourth and fifth lumbar vertebrae with some associated vertebral sclerosis. Laminectomy was performed with the removal of the laminae of L4 and L5. The epidural fat was replaced by a metastatic carcinoma encircling the dura. While recovering from surgery, a peach-sized subclavicular mass on the left chest wall developed. Treatment consisted of postoperative x-ray therapy to the lumbar region, and systemic combination chemotherapy, thio-TEPA and Methotrexate. Marked regression of the subclavicular mass occurred when the antifol stomatitis appeared. She was discharged on October 24, 1960, after showing marked improvement in her general clinical status. Maintenance thio-TEPA was continued for the ensuing one and a half years, together with three courses of Methotrexate, each to the point of minimal stomatitis. The

white blood count was maintained in the range of 2,000 to 4,000/cu mm. At no time was there any significant clinical purpura or bleeding. At the end of a year and a half of chemotherapy, she began to develop profound anemia, associated with recurrence of the subclavicular nodule. This local lesion again regressed after a fourth course of Methotrexate, but her anemia persisted. The chemotherapy was stopped and two whole blood transfusions were given. The anemia subsided within one month, on iron, vitamins, and testosterone

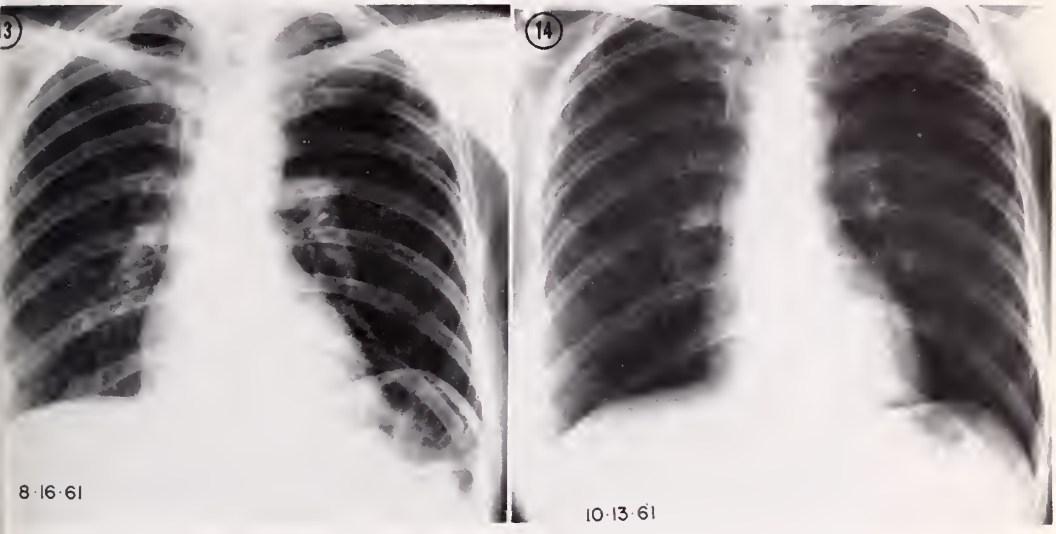

FIG. 13. Left lateral infraclavicular metastasis prior to combination chemotherapy (Case #4).

FIG. 14. Status 2 months after thio-TEPA and Methotrexate combination showing regression of pulmonary metastasis.

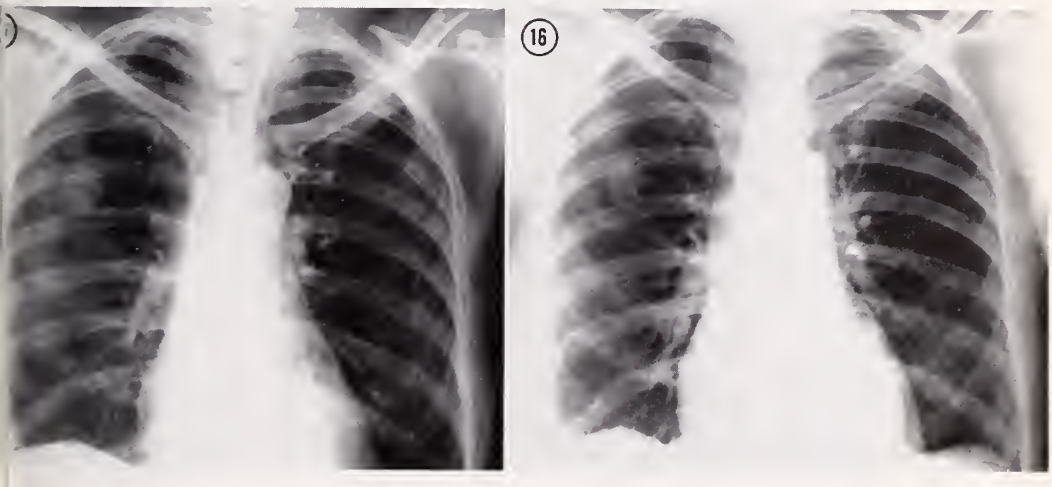

FIG. 15. Solitary pulmonary metastasis (Case #6) in right lung between second and third rib anteriorly.

FIG. 16. Progressive shrinkage in lesion shown 3 weeks after starting combination chemotherapy.

therapy. She remained in remission off chemotherapy for three months, but then developed pulmonary metastases, which currently have shown partial regression on Cytoxan therapy.

Case 6

A 54 year old spinster developed a single right midlung parenchymal metastasis and several right supraclavicular metastases 2½ years after right mastectomy had been performed. Menopause had occurred four years previously but vaginal smear revealed residual estrogen effect. She was given two months of aqueous crystalline testosterone therapy, 450 mg per week with resulting masculinization but no change in supraclavicular or pulmonary metastases (Fig. 15) which formed a group of nodes 3 x 3 cm. Priming thio-TEPA, 60 mg in four days, was then given intramuscularly with 7.5 mg Methotrexate, orally for seven days. A mild stomatitis with some nausea was sustained for several days but subsided uneventfully. Three weeks after initiating the combination chemotherapy, chest x-ray (Fig. 16)

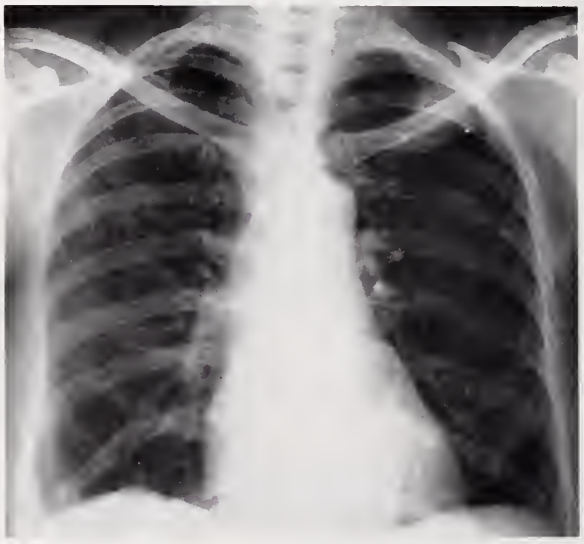

FIG. 17. Progressive shrinkage in lesion shown 7 weeks after starting combination chemotherapy.

showed definite reduction in the size of pulmonary metastasis. The supraclavicular nodes had regressed almost completely. The leukocyte count was 4,300 and there were adequate platelets on peripheral smear. Maintenance thio-TEPA, 15 mg per week, intramuscularly was begun in the third week of therapy together with a second course of Methotrexate at the same dosage as in the first course. Seven weeks after starting the combination, the pulmonary lesion had almost disappeared (Fig. 17) and the supraclavicular mass was no longer palpable. The white blood count remained slightly leukopenic with adequate platelets and no anemia. The patient was placed on a routine of 15 mg of thio-TEPA every ten days. She was also maintained on 100 mg of aqueous crystalline testosterone every ten days. At the time of this report, six months after onset of cytotoxic chemotherapy, there is no evidence of recurrence.

Case 7

A 55 year old spinster appeared with a large, fungating ulcerated primary carcinoma of the right breast, of at least three years' duration (Figs. 18, 19). This tumor mass infiltrated the entire right breast and axillary fold, but did not involve the supraclavicular fossa

FIGS. 18 and 19. Status of large fungating ulcerating carcinoma in Case #6 prior to thio-TEPA-Methotrexate therapy.

FIGS. 20 and 21. Almost total shrinkage and flattening of large fungating tumor mass plus marked reduction in numerous nodular masses within major breast tissue. Four courses of Methotrexate had been given with the patient on maintenance thio-TEPA during a four month period.

grossly. Surgical biopsies revealed infiltrating scirrhous carcinoma (Dr. S. Otani). Surgical consultant deemed the lesion unresectable in its presenting form. The patient showed severe cancerphobia, fear of surgery, profound mental depression and guilt over this neglected lesion. Menopause had occurred four years previously.

A course of combination chemotherapy with simultaneous thio-TEPA and Methotrexate was begun on June 19, 1962. The full priming dose of 60 mg of thio-TEPA was given, followed after three weeks by maintenance thio-TEPA, 15 mg, intramuscularly every seven to fourteen days to maintain a slight leukopenia. The first course of Methotrexate was given simultaneously with the initial priming doses of thio-TEPA. These dosages consisted of 7.5 mg of Methotrexate orally for four days followed by 10 mg for the subsequent three days. The typical stomatitis appeared on the eighth day after starting the oral Methotrexate. At the height of this initial antifol reaction, the white count was 3,200 cells per cu mm and the tumor masses had begun to shrink visibly in size. A second course of Methotrexate was begun on July 17, four weeks after the first course. The third course of Methotrexate was given on August 16, and the fourth course on September 2nd. The shrinkage of tumor masses was progressive and dramatic. The large fungating pedunculated tumor appendage gradually disappeared without development of slough or any significant bleeding (Figs. 20, 21). The ulcerating lesions epithelized, and the edema subsided. Satellite nodules in the axilla and axillary fold disappeared after the second course of Methotrexate.

The patient's hair thinned but there was no clinical alopecia. The patient's blood count remained satisfactory throughout the entire four months of thio-TEPA and Methotrexate therapy. The lowest hemoglobin was 12 Gm and the least white count was 3,200 without any accompanying purpura or thrombopenia. The thinning of the hair which occurred after the second course of Methotrexate subsided completely within four weeks after stopping the Methotrexate. During the four month course of chemotherapy, the patient was given much psychological support. She next completed a course of cobalt radiation therapy in preparation for surgery which she at last accepted. Radical mastectomy was performed uneventfully on December 20, 1962.

DISCUSSION

The value of cytotoxic chemotherapy for disseminated or recurrent metastatic breast carcinoma has not been clearly delineated in the clinical literature. Until recently, the extensive use of cytotoxic agents was more or less interdicted by the twenty to thirty per cent incidence of palliative regression obtainable from the relatively less toxic endocrine methods of control. As recently as 1960, the authoritative text of Pack and Ariel failed to mention cytotoxic chemotherapy as an accepted modality of treatment for the advanced metastatic patient. The response rate of 60 per cent among our forty patients after combined chemotherapy, with 38 per cent remaining in remission more than six months and 20 per cent surviving more than a year in remission, compares favorably to endocrine therapy, especially since almost all of these patients were suffering from far advanced disease resistant to hormonal therapy. Thio-TEPA and Methotrexate are capable of inducing a significant number of objective responses whether or not there has been previous response to oophorectomy, testosterone or radiation.

Inhibition of metastatic growth as the result of thio-TEPA and Methotrexate usually begins 8 to 10 days after initiating the drugs in simultaneous combination, *i.e.*, a few days after the onset of the stomatitic antifol symptoms. If the neoplasm has not begun to respond by the time the thio-TEPA effect occurs, namely, three weeks after the combined priming dosages had been started, our

experience indicates that there is no likelihood of a subsequent delayed response. This relatively short period of one to three weeks necessary to observe the initial effects of combined chemotherapy stands in contrast to the several months usually needed to evaluate estrogen or androgen therapy. There seems little reason to initially prefer cytotoxic agents to hormones in slow-growing metastatic disease. The more rapidly metastasizing lesions, especially in the patients below age 55, probably warrant the combined use of hormones (androgens) with the thio-TEPA-Methotrexate combination.

The relative safety of the cytotoxic antifol-alkylating agent combination was evident among our females with breast carcinoma as among the women in our recent series of advanced ovarian carcinomas (22). Only three patients showed unexpected or life impairing toxicity, and in only one poor risk patient was a fatality precipitated. A better predictive evaluation of the bad risk patients might have obviated even these cases of toxicity. Most patients who responded to therapy were more than willing to again risk the stomatitic or alopecic side effects and other inconveniences from subsequent courses of therapy. Usually, the subjective toxicity of subsequent courses of the antifol was better tolerated because of a more precise interruption of drug. It is our impression that the toxicity of the Methotrexate during thio-TEPA maintenance was distinctly better tolerated and more predictable than the toxicity of 5-Fluorouracil.

The average female with advanced metastatic breast carcinoma tolerated about 0.8 to 0.9 mg of antifol/kg per week in divided daily oral doses before reaching the first clinical signs of folic acid deficiency. This aggregate dose is considerably lower than the dosage needed to induce the antifol response in younger females with choriocarcinoma (26). Previous androgen and radiation therapy and age differences in breast patients may account for this lower average aggregate weekly dose. More striking from the pharmacologic viewpoint was the wide range of Methotrexate dosage (0.4 mg to 1.5 mg/kg/week in daily divided doses) required to titrate our patients into clinically similar antifol toxic states. The endogenous systemic folic acid reserves of the poor risk, emaciated patient evidently were so low as to require as much as a 50 to 75 per cent reduction in the weekly aggregate dosage to safely employ Methotrexate, a fact not clearly delineated in the chemotherapy literature. Among several hundred patients with various neoplasms, we have seen one patient who repeatedly showed antifol toxicity with doses as low as 0.2 mg/kg/wk. Patients with profound anemia, protracted fever or impaired renal function, azotemia, recent antibiotics or prednisone therapy, strenuous diuretics, and prolonged intravenous fluid administration without adequate oral ingestion of food were decidedly less tolerant to antifols. The adrenalectomized patient on maintenance steroids also showed an unusual sensitivity to the antifol effect. It is our impression that although androgens may lower the antifol tolerance somewhat, they provide myelostimulative support for the hematopoietic system while the patient is on cytotoxic combination chemotherapy. This appears to contrast with corticosteroid action which although also reducing tolerance to antifols, probably enhances the excretion as well as utilization of folic acid and its pre-

cursors. It has been our policy most recently to continue the administration of aqueous crystalline testosterone in patients who have previously been on androgen therapy, but to postpone corticosteroid therapy as long as possible while administering the thio-TEPA-Methotrexate combination.

Overt resistance to Methotrexate and thio-TEPA with rapid recurrence of metastases may be observed in a previously responsive tumor as early as three to four months after the initial complete gross regression of metastases. Although 60 per cent of the cases in our series showed the initial objective response to the combination, only 20 per cent were able to remain in remission for more than a year while continuing on vigorous chemotherapy. This emphasizes the intense need for study of other drug combinations in an attempt to thwart drug resistance. Among our combination-resistant cases, there were

TABLE 4

Chemotherapy Responses Advanced Breast Carcinoma

Agent	No. Cases	% Response	Source
MTX	36	29	Wright
MTX	70	31	Combined
TP + MTX	40	60	Greenspan
TP	252	63	Bateman
TP	89	39	Sears
TP	18	55	Gurling
Cytox	24	25	Coggins
Cytox	20	30	Stoll
5-FU	17	86	Ansfield
5-FU	20	60	Hurley
5-FU	28	30	Vaitkevicus
5-FU	43	42	Kennedy
5-FU	38	37	Weiss
5-FU	22	50	Ivy

several cases of short-term (one to three months) partial regression of metastases after Cytoxan or 5-Fluorouracil, but there were no sustained regressions comparable to the initial response to thio-TEPA and Methotrexate. A comparison of our results of thio-TEPA-Methotrexate therapy with those using single cytotoxic agents is difficult, not only because of variation in clinical material and criteria for response, but also because of differences in the willingness of various investigators to induce and cope with serious drug toxicity. Table 4 summarizes some representative reports of the responses to four different cytotoxic agents. In a recent paper from the Mayo Clinic, Ivy reported that 5-Fluorouracil induced fifty per cent subjective or objective responses in 22 cases of far advanced breast cancer. After obtaining objective regression in 5 of 22 cases for seven months or longer with 5-Fluorouracil, Ivy concluded that, "No other chemotherapeutic agent available has achieved this percentage or duration of clinical responses." Our results with thio-TEPA plus Methotrexate appear distinctly

better in terms of development and maintenance of objective regression. It is also evident from the literature that the response rate to the relatively less toxic thio-TEPA alone is equal to or better than to 5-Fluorouracil.

Responses to 5-Fluorouracil are usually of relatively short duration when obtained, and have been accompanied by a 6 to 30 per cent induced mortality. Responses to Cytoxan have been well below 50 per cent, with a duration of remission considerably less than that reported in our present series for thio-TEPA and Methotrexate. Although the response rate of 60 per cent to combination chemotherapy is not strikingly better than what might have been expected from thio-TEPA alone, the most encouraging aspect has been the degree, rapidity and duration of tumor inhibition with the Methotrexate-thio-TEPA combination in advanced disseminated metastatic disease in which formerly no palliation could be expected after failure of hormonal methods.

SUMMARY

Forty patients with advanced breast cancer were treated with full simultaneous doses of thio-TEPA and Methotrexate. Most of these cases presented with resistant or recurrent metastatic disease after postoperative radiation therapy, oophorectomy and androgen therapy. The combination chemotherapy was continued with maintenance doses of thio-TEPA accompanied by repeated courses of Methotrexate. Sixty per cent of these patients showed objective tumor regression and objective clinical improvement within two to four weeks after onset of chemotherapy. Thirty-eight per cent showed excellent (total regression) or good (substantial regression) of observable metastases and remained in remission for six months. Twenty per cent showed sustained remission for more than one year. Regression occurred in about two-thirds of cutaneous, subcutaneous, pulmonary and pleural metastases, usually at the height of the antifol (Methotrexate) effect. Five of eight cases of cerebral metastases disease responded to skull radiotherapy given with simultaneous combination chemotherapy for extracerebral metastases. Response in bone lesions and regression of metastatic hepatomegaly occurred less often. Some toxic effects were induced in all patients but only three patients developed severe, unexpected, life impairing toxicity. One induced fatality occurred in a poor risk patient. The stoichiometric aspects of Methotrexate dosage in relation to the clinical risk category of the patient were important in avoiding frequent serious toxicity.

The role of radiotherapy and hormone therapy, in conjunction with the cytotoxic combination was discussed. The use of thio-TEPA and Methotrexate in advanced metastatic breast carcinoma appeared reasonably safe and clinically rewarding.

Acknowledgment

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RADIOLOGICAL NOTES

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CASE NO. 204

A six year old female was admitted to the hospital for evaluation of a pelvic mass.

One week prior to admission the patient was seen by her family physician for examination following a short self-limited episode of nausea, vomiting and low-grade fever. The child was asymptomatic at the time of the initial examination, but a soft suprapubic mass could be palpated to the left of the midline. This was confirmed by bimanual palpation (rectal-abdominal). The mass persisted following catheterization of the bladder. The remainder of the physical examination and the past history were entirely noncontributory.

Routine examinations of the blood and urine were normal. Plain film study of the abdomen showed an orange-sized soft tissue mass in the pelvis to the left of the midline. A small irregular calcification was noted in relation to the upper right lateral portion of the mass. The diagnosis of teratoma of the left ovary was proposed. Intravenous urogram showed a left hydronephrosis and hydroureter with obstruction to the left ureter at the pelvic inlet in relation to the pelvic mass. Combined barium enema and cystogram were performed (Figs. 1A, B, and C). The rectosigmoid was displaced posteriorly and the sigmoid superiorly, and the bladder was displaced to the right and anteriorly. Opacification of these pelvic viscera afforded exquisite localization and delineation of the mass itself. At laparotomy, a large smooth-walled cyst of the left ovary was identified and resected without incident. Histologic examination revealed a benign teratoma.

DISCUSSION

Teratomas constitute over fifty per cent of ovarian tumors in children, but only 10 to 15 per cent of ovarian neoplasms when all age groups are included (2, 4). They are extremely rare before the age of three, although such a tumor in a 16 month old female has been documented (5). In general, teratomas are cystic in nature and benign histologically. A small percentage undergo malignant degeneration in the older age groups, but malignancy before the age of puberty is extremely rare (2). Solid teratogenous tumors, a much less common variety, are considered to be of high potential malignancy (1, 2).

The lesion may be discovered because of enlargement of the abdomen, or a mass may be discovered on routine examination in the asymptomatic patient. Gastrointestinal or urinary symptoms secondary to pressure may occur. Tortion of the tumor, the most common complication (4), is a well-known cause for an

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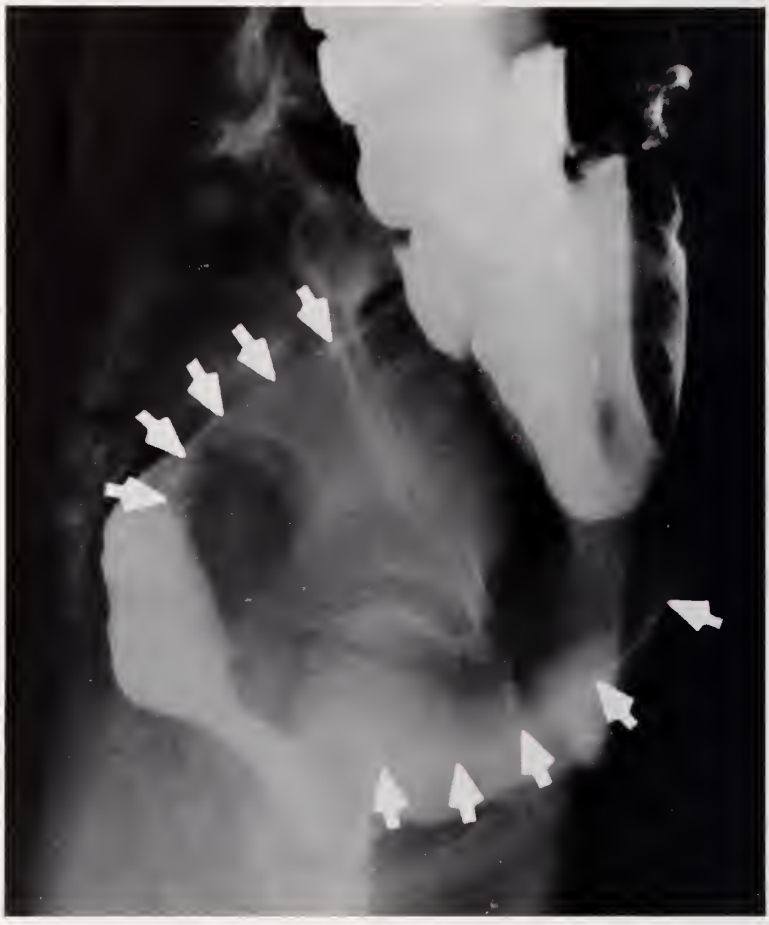
acute abdominal emergency in children (3). It is sometimes forgotten that repeated self-limited attacks of tortion may give rise to a clinical picture of chronic or recurrent abdominal pain. An infrequent complication has been called "derm-

Case 204, Fig. 1A. Antero-posterior view of the abdomen during a combined barium enema and cystogram shows the bladder filled with water soluble opaque material and the colon with barium. The soft tissue mass on the left side of the pelvis exerts extrinsic pressure on the bladder (arrows). The sigmoid is draped over the mass.

oid cyst peritonitis," and is due to leakage of the cyst contents into the peritoneal cavity resulting in a granulomatous reactive peritonitis. The differential diagnosis in this rare situation includes abdominal carcinomatosis and tuberculous peritonitis (4, 5).

On physical examination, although the mass often can be palpated abdominally, careful bimanual examination should not be neglected (rectal-abdominal).

The examination should be repeated following catheterization of the bladder to rule out bladder outlet obstruction. The hymen should be inspected to search for possible hydrocolpos. Signs of disseminated malignant disease may be present in the unusual case.

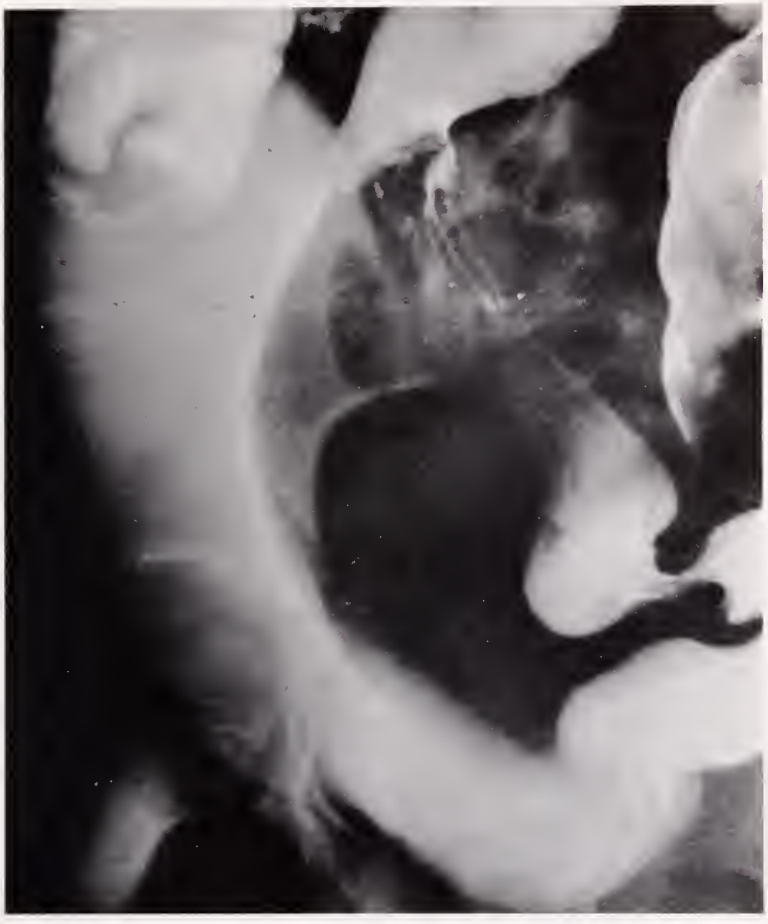


Case 204, Fig. 1B. Lateral view shows anterior displacement of the bladder (anterior arrows) and posterior displacement of the rectum (posterior arrows).

Specific radiographic features, in addition to the usual appearance of soft tissue mass, include calcifications related to the mass and a radiolucent quality to the mass. Calcification of some type occurs in 50 to 75 per cent of cases and may represent teeth, calcified cartilage, true bone formation, or calcification in the cyst wall (2, 3). Radiolucency is only occasionally clearly demonstrable and is due to the high fat content in the sebaceous material contained within the cyst. Intravenous urography is indicated to establish the relationship of the

tumor to the urinary tract. Combined barium enema and cystogram offers the opportunity of delineation of the extent of the mass, as in the case presented.

Case Report: Benign teratoma of the ovary in childhood.



Case 204, Fig. 1C. Right posterior oblique projection again demonstrates the prominent indentation on the bladder contour.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. Richard J. Sullivan and Alfred S. Moscarella, Good Samaritan Hospital, Suffern, New York.

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CASE NO. 205

A three month old female infant was admitted to the hospital with a history of failure to void and progressive enlargement of the abdomen for twelve hours prior to admission. The patient was well until three days prior to admission when mild diarrhea developed. The diarrhea seemed to be subsiding uneventfully, but on the morning of the day of admission the mother noted enlargement of the abdomen which progressed to marked distention.

Physical examination revealed marked abdominal distention but a specific mass was not outlined. Bowel sounds were normal. An attempt was made to catheterize the bladder but the urethral orifice could not be located.

Plain film study of the abdomen showed soft tissue masses occupying the lower half of the abdominal cavity and bulging the flanks. Intravenous urogram showed considerable delay in excretion but with progressive opacification of the urinary tracts. At nine hours after injection of opaque material a massive bilateral hydronephrosis and hydroureter could be seen. The ureters were tortuous and the lower ends of the ureters appeared elevated. No opacification of the bladder had occurred and the patient had not voided in the interim (Fig. 1A).

The patient was then examined under anesthesia in the lithotomy position. The urethral orifice was located on the anterior wall of the vagina at the introitus. Some inflammatory exudate was seen about the meatus, which was pinpoint in size. The exudate was removed, the urethra dilated, and the bladder catheterized and emptied of 500 cc of urine. The vagina was not investigated at this time.

A cystogram was then performed which showed displacement of the bladder to the right. The lower ends of the ureters were opacified with opaque material excreted from above and again showed elevation (Fig. 1B). The working clinical diagnoses at this time were bladder neck obstruction secondary to an undiagnosed pelvic mass plus an abnormal urethral course with urethral stricture.

Because of the marked loss of functioning renal parenchyma, bilateral nephrostomies were performed. In the postoperative period, electrolyte imbalance was successfully managed with parenteral fluids, and urinary tract infection was controlled with appropriate antibiotic therapy. The nephrostomies func-

Case 205, Fig. 1A. Antero-posterior film of the abdomen made nine hours after the start of an intravenous urogram shows massive bilateral hydronephrosis and hydroureter. The lower ends of both ureters are displaced upwards. There is no opacification of the bladder.

Case 205, Fig. 1B. Antero-posterior film of the abdomen was made shortly after "A" following catheterization and introduction of opaque material into the bladder. The bladder is displaced to the right (arrows). The left lower ureter is displaced upwards.

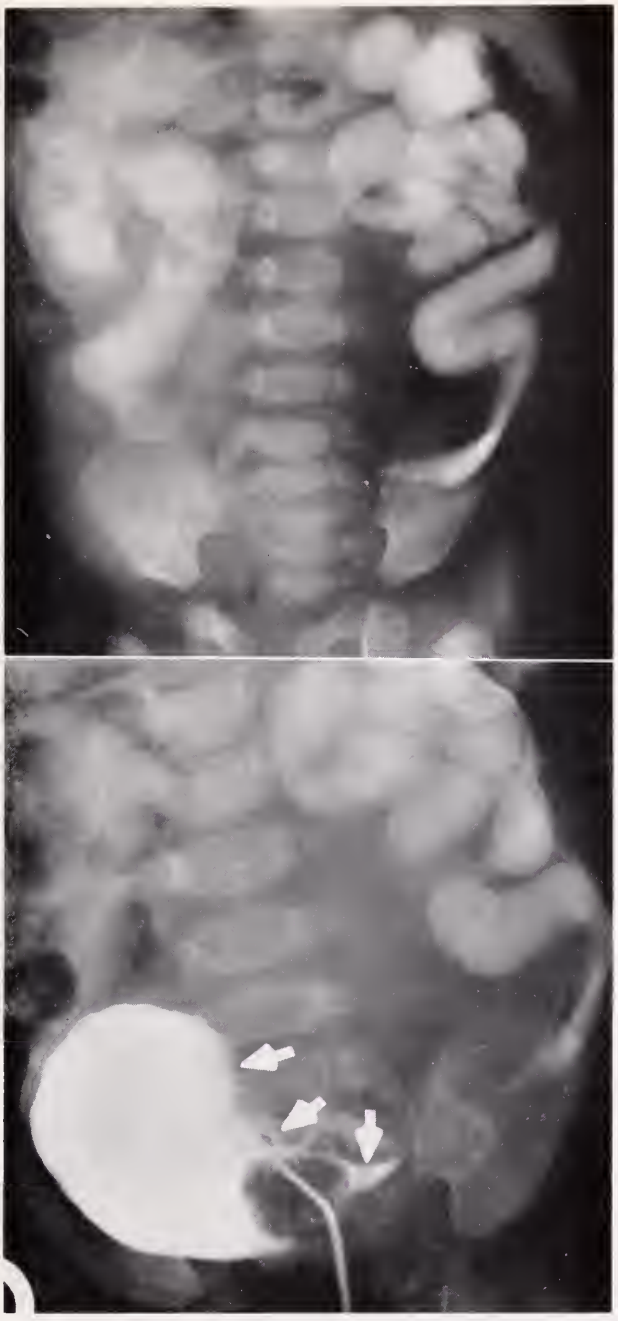


Fig. 1A (top). Fig. 1B (bottom).

tioned satisfactorily but almost no urine was passed from below. The urethra was dilated on two occasions but a third attempt at dilatation was unsuccessful. Six weeks following admission the patient was again examined under anesthesia. The urethral meatus was located on the anterior vaginal wall at the introitus. The hymen was not identified. Vaginoscopy revealed a short cavity proximal to the introitus limited internally by an oblique membrane. The cervix was not identified within this cavity. Bimanual examination (rectal-abdominal) revealed a well-defined cystic mass approximately 10 cm in diameter just proximal to the short vaginal cavity. The mass deflected the bladder sharply upward and anteriorly and accounted for the unusual course of the urethra. A specific diagnosis of hydrocolpos was now advanced. The posterior vaginal membrane was punctured from below on two occasions but no fluid or material was forthcoming.

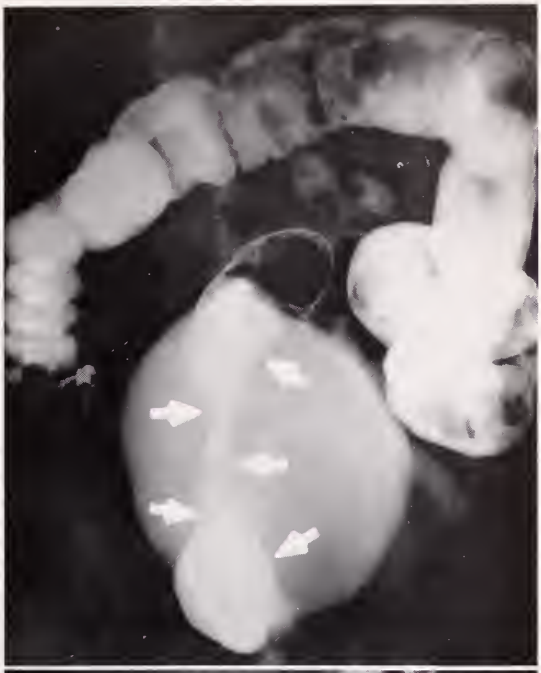
The patient continued to thrive. Two months later additional radiographic studies were performed, including nephrostomy pyelograms, cystogram and barium enema. Dilatation of the upper tracts and ureters was again noted, similar to that on the original studies. Combined barium enema and cystogram clearly outlined the pelvic mass (Figs. 2A and 2B). In the frontal projection, the rectum was narrowed and the sigmoid elevated. Residual opaque material in the lower left ureter showed the elevation of this structure as well. In the lateral view there was a clear hiatus between the rectum and the bladder with narrowing of the rectum.

Laparotomy was performed and a 10 cm cystic mass was found which filled the true pelvis somewhat more on the left than on the right. The walls of the mass were thick and leathery. The uterus was displaced anteriorly and superiorly and the bladder was displaced anteriorly and to the right by the mass. The ureters were thick-walled and were intimately adherent to the walls of the mass on each side; they were dissected free. The mass was incised posteriorly and a large quantity of thick, gray-white, cheeselike material was evacuated. The cavity was inspected and the inferior limiting membrane was then divided. The uterine cervix could be seen to open into the cavity thus establishing the cystic structure as the vagina. The posterior incision was closed and a catheter was left *in situ* draining the vagina from below.

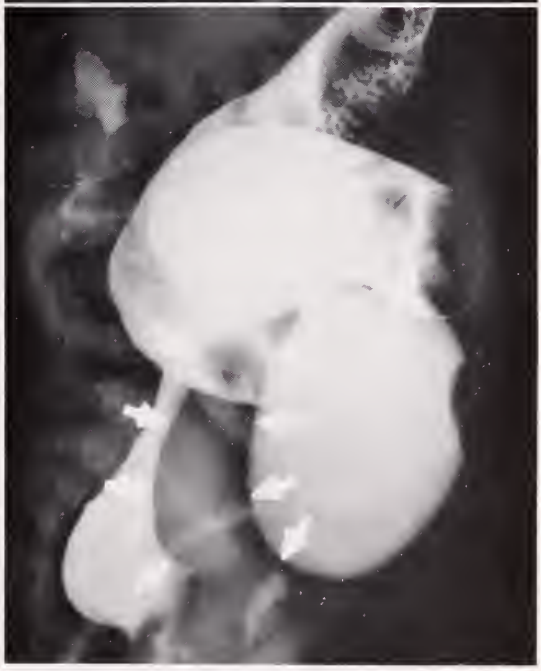
The postoperative course was a smooth one. Regular vaginal irrigations were performed. There was progressive diminution in urinary excretion through the left nephrostomy which then closed spontaneously after removal of the tube. The right nephrostomy continued to function and a right nephrostomy pyelogram was performed one month postoperatively. Hydronephrosis and hydroureter again were noted but there was drainage of opaque material into the bladder during the study.

DISCUSSION

Hydrocolpos results from a combination of two distinct abnormalities. The first abnormality is a developmental one and is due to the presence of vaginal outlet obstruction. In some cases the obstruction is due to an imperforate hymen (5). In most cases, however, the obstruction is due to an abnormal membrane



Case 205, Fig. 2A. Postero-anterior view of the abdomen shows the bladder opacified with water soluble opaque material and the colon with barium. The rectum is narrowed (arrows). The sigmoid is draped over the mass. Opaque material is seen in the left urinary tract.



Case 205. Fig. 2B. Lateral view during the same examination shows a hiatus between the rectum and the bladder. The bladder is displaced forwards (anterior arrows) and the rectum backwards (posterior arrows).

or diaphragm (imperforate vagina) which lies above the expected position of the hymen (3, 6). The condition may represent a failure of canalization at the junction of the cephalad portion of the vagina (embryologically from the Müllerian duct system) and the caudad portion (embryologically from the urogenital sinus) (8). The membrane can occur at any level in the vaginal canal and may be very thin or quite thick. Complete vaginal agenesis or atresia may occur but this is rare (2, 4).

The second requirement for the production of hydrocolpos is the presence of large quantities of secretions from the uterine cervix. The secretions apparently are in response to high titers of maternal estrogenic hormones. There appears to be great individual variation in the degree of hormonal stimulation. This may account for the puzzling fact that in patients with imperforate hymen it is much more common for hematocolpos to develop at puberty than for hydrocolpos to develop in the newborn infant (3). As far as terminology is concerned, the term hydrometrocolpos is preferred by many authors since the uterus may share in the cystic dilatation (3, 6); nevertheless, uterine dilatation is not prominent in most cases and in these the term hydrocolpos is quite accurate anatomically (2). Hematometrocolpos in the newborn is extremely rare (1).

Clinical symptomatology is usually referable to a large or enlarging abdominal mass usually discovered at birth or in the neonatal period, or by obstruction to urinary outflow. The tumor may be huge and fill the entire abdomen or the abdomen may be filled with a combination of tumor and dilated urinary tracts. Physical examination should include not only abdominal palpation, but bimanual examination (rectal-abdominal) and careful inspection of the external genitalia. The examination should be repeated after catheterization of the bladder which eliminates the latter as a possible cause of the mass. Catheterization may be difficult or impossible due to distortion of the anatomy secondary to the large mass. The diagnosis may be established by inspection if an imperforate hymen or membrane is observed which is bulging or which bulges with suprapubic pressure. However, this finding may be absent in those cases where the membrane is located more proximally. Vaginoscopy must then be performed in order to observe the short vagina, abnormal membrane, and the absence of the cervix at the vault.

Once the diagnosis is established, treatment should be instituted immediately and directed toward removing the vaginal outlet obstruction. In favorable cases simple incision or excision of the hymen or membrane may be sufficient to relieve all symptoms. Laparotomy is indicated when the membrane is proximal and thick, when vaginal agenesis or atresia is present, when vaginal drainage from below has been unsatisfactory or when urinary obstructive symptoms have persisted.

The case described illustrates many of the radiographic features, i.e. pelvic-abdominal mass, obstructive uropathy, and displacement of adjacent viscera. Further, the extent of the mass was remarkably well delineated by combined cystogram-barium enema examination. A more direct and absolutely definitive radiographic procedure is the introduction of opaque material into the cystic

mass (3, 6, 7). This procedure may delineate not only the vagina itself but the uterine cavity in continuity as well. Differential diagnosis should include other causes of pelvic mass in this age group such as ovarian and para-ovarian tumors, urogenital and intestinal duplications, mesenteric, urachal and Gartner's duct cysts, intrinsic urinary tract obstruction, anterior meningocele, presacral tetratoma and lymphoma (6). Clinical awareness of the problem and appropriate examination should lead to the correct diagnosis.

Case Report: Hydrocolpos with obstructive uropathy in infancy.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. F. Yandel and M. Aria, Good Samaritan Hospital, Suffern, New York.

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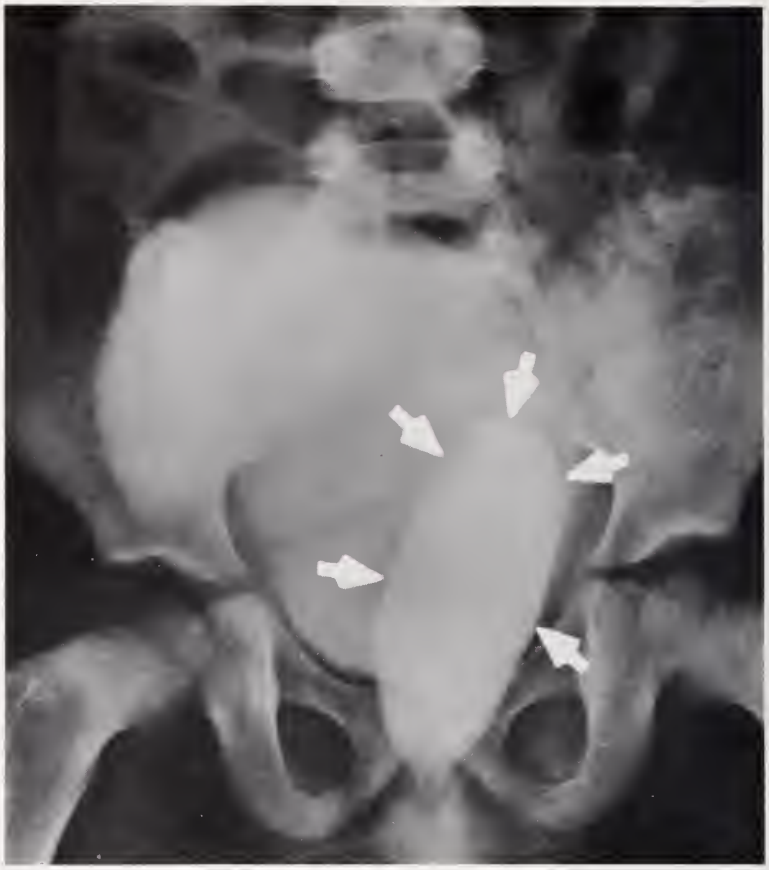
CASE NO. 206

On routine examination, a three year old boy was noted to have hypospadias and a bifid scrotum. The child was the product of a normal pregnancy and had developed well during infancy. Examination revealed a well-developed, well-nourished boy who was vigorous and alert. The genitalia revealed a small phallus with a moderately severe chordee and a hypospadias with the urethral meatus at the junction of the scrotum and penis. Both testicles could be palpated within the bifid scrotum. Laboratory examinations were negative. Buccal smears showed cells with a male sex chromatin pattern. Intravenous pyelogram revealed normal upper urinary tracts. Cystourethrogram demonstrated two separate dye-filled structures, one narrow and elongated and the other larger and rounder (Fig. 1). The former filled first and only after complete filling did the latter visualize. The smaller of the two structures represented a Müllerian duct remnant, namely a blind vaginal pouch, and the larger rounded one represented the urinary bladder. The patient had a Z-plasty operation on the chordee and a repair of the hypospadias. No surgical removal of the vaginal pouch was attempted.

DISCUSSION

This case represents an example of male pseudo-hermaphroditism with both testes situated within the scrotum and a vaginal pouch communicating with a urogenital sinus. Cases of male pseudo-hermaphroditism are subdivided into



Case 206, Fig. 1. Cystourethrogram reveals contrast medium outlining a long, relatively narrow cavity (arrow) as well as a second larger, more rounded organ. The former represents the vaginal remnant and the latter the urinary bladder. Contrast medium enters the urinary bladder only after the vaginal pouch is completely filled.

those with external genitalia resembling males or of ambiguous sex, and those with external genitals simulating females. The present case falls into the former category. Such cases usually present with an extreme form of hypospadias and the scrotum is always bifid. The testes may be either extra-abdominal, within the inguinal canal, or truly intra-abdominal. In a large series of cases, eighty per cent had no palpable testes within the scrotum (1). When no testis is found, a fallopian tube tends to be present on the side of the absent testis. In two large series of male pseudo-hermaphrodites, two-thirds had external genitalia of the

male type and one-third of the female type (2). When there is a common urogenital sinus, as in the present case, the vaginal pouch opens into the posteroinferior portion of the sinus. On occasion, however, the vaginal pouch opens independently into the perineum just behind the urethra. It is in this situation that a carefully performed cystourethrogram is of prime importance in demonstrating the size and position of the Müllerian duct remnant, rendering corrective surgical management easier and more accurate.

Case Report: Male pseudo-hermaphrodite with a vaginal pouch entering a urogenital sinus.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. Joseph M. Silagy and George Ginandes.

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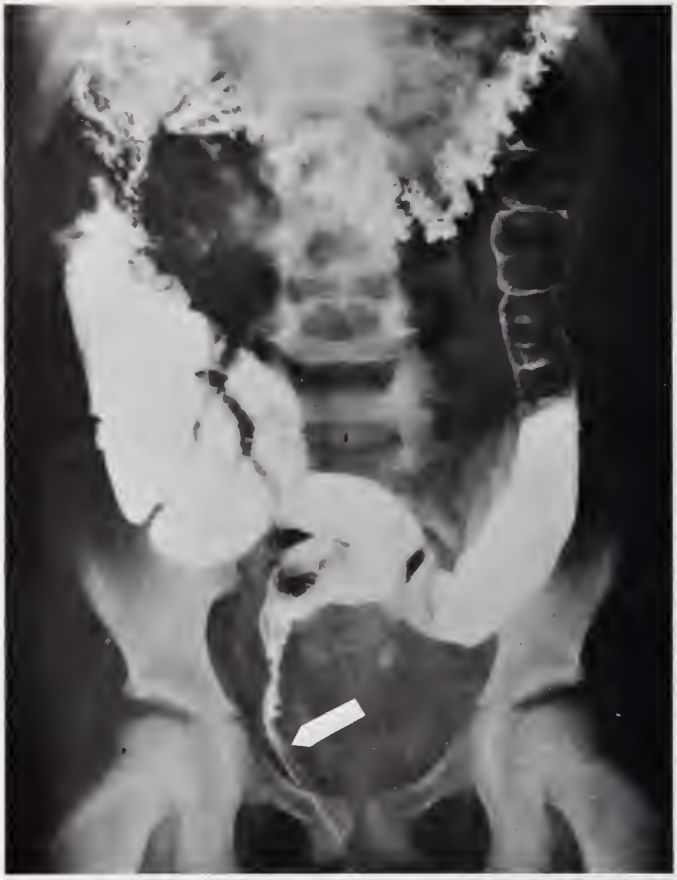
CASE NO. 207

This 5½ year old girl had a one month history of pain in the left buttock with a low-grade fever and dysuria. The patient had been treated for a urinary tract infection with oral antibiotics without relief of symptoms. Intravenous pyelogram was said to be normal. White blood cell count showed a moderate leukocytosis with a shift to the left. The sedimentation rate was 60 mm per hour. X-rays of the pelvis and spine were normal. All cultures of the blood and stools were also normal. One week before admission, the patient's fever spiked to 102° and for the first time, rectal examination revealed a mass on the left side of the pelvis. Abdominal examination was negative. Gastrointestinal series and barium enema were then performed. The gastrointestinal series and small bowel examination were negative. Barium enema showed a smooth mass in the left side of the pelvis, displacing the rectum and rectosigmoid to the right (Fig. 1). The patient was hospitalized and a laparotomy was performed. At operation, a 5 x 7 cm cystic mass was found deep within the broad ligament in the left paravaginal area. Needle aspiration of the mass revealed the presence of thick greenish pus and the abscess was drained through the vagina. Because of its location and appearance, the abscess was regarded as arising in a Gartner's duct cyst. Follow-up examinations over the next eighteen months revealed the child to be entirely well with no evidence of a recurring pelvic mass. There was some residual thickening of the left side of the retrovaginal system and a small amount of drainage per vagina.

DISCUSSION

Gartner's duct is an embryonic remnant arising from the Wolffian duct. The vestigial Wolffian duct courses in the mesosalpinx as Gartner's duct and then ex-

tends downwards first lateral to the margin of the uterus and then along the antero-lateral wall of the vagina (1). As a result of distention of imperfectly obliterated portions of the duct, cysts may arise in various portions of its course.



Case 207, Fig. 1. Postero-anterior film in the course of a barium enema reveals a smooth round soft tissue mass in the left side of the pelvis causing a well-circumscribed extrinsic pressure defect on the left lateral aspect of the rectum and rectosigmoid (arrows). There is no evidence of mucosal alterations of the barium-filled rectum and rectosigmoid. No abnormal calcifications are noted within this mass. There appears to be no dilatation of the colon proximal to this mass.

In the vaginal segment therefore, Gartner's duct cysts are always found in the antero-lateral portion of its wall. Such cysts may be segmented or multiple. Usually Gartner's duct cysts are small in size, but occasionally present as large tense masses in the vagina simulating cystoceles (2). On occasion, Gartner's duct can be outlined by hysterography as a fine linear stricture in the para-vaginal and parametrial regions. As in the case described, when cysts form and

attain large enough size, they displace adjacent pelvic organs. In a young female, the finding of a smooth cystic mass located anterior to the rectum and behind the urinary bladder deep within the pelvis should suggest the diagnosis of Gartner's duct cyst.

Case report: Gartner's duct cyst with abscess formation.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. Donald Gribetz and Jerrold M. Becker.

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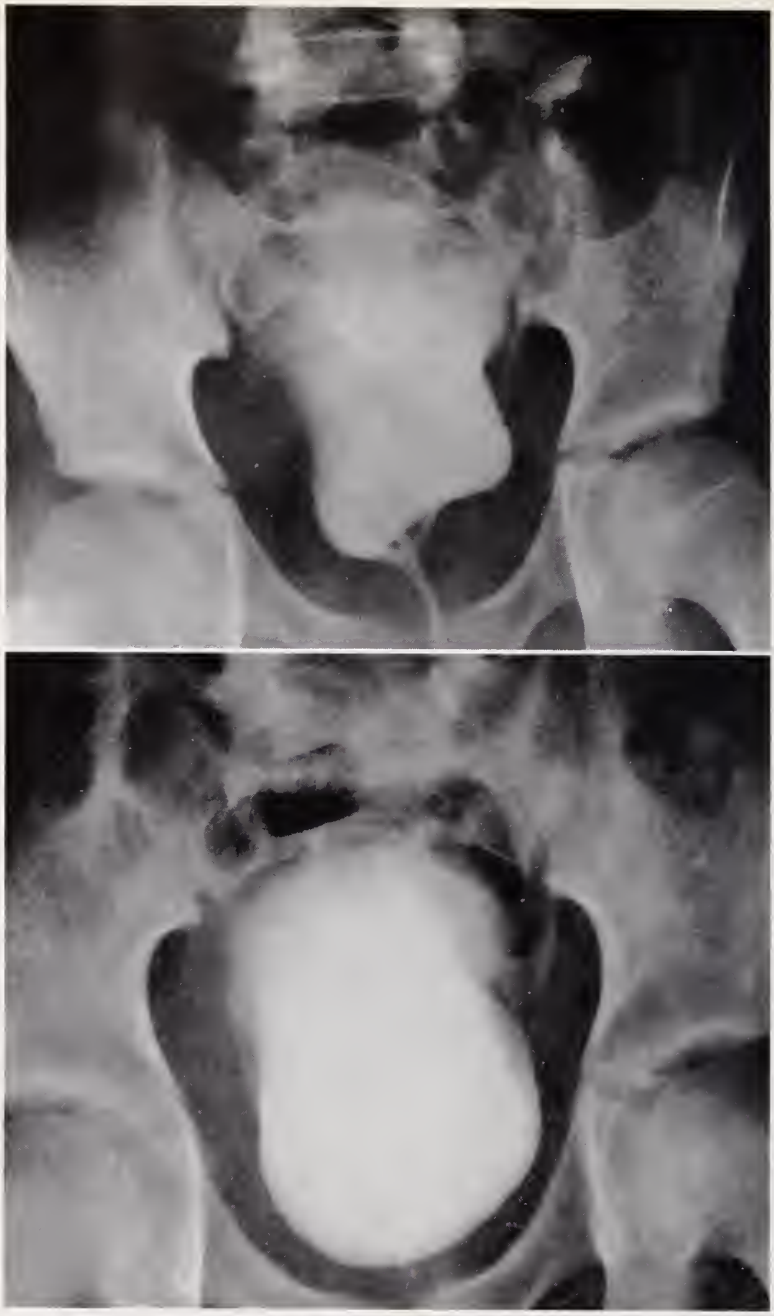
CASE NO. 208

An 11 year old boy was admitted with a four week history of difficulty in urination, swelling of the left lower extremity and marked enlargement of the scrotum. The patient experienced no pain, fever, weight loss or hematuria. Physical examination revealed a large, lobulated, non-tender mass filling the pelvis and reaching to just below the umbilicus on the left side. The mass extended downwards to the left side of the scrotum and displaced the median scrotal raphe to the right. Rectal examination revealed a hard, nodular mass in the left lobe of the prostate continuous with the pelvic tumor. Numerous enlarged hard inguinal lymph nodes were palpated bilaterally. The left lower extremity was massively edematous and a number of dilated veins were noted on the upper portion of the thigh. Intravenous pyelography revealed normal upper urinary tracts. The lower portions of both ureters were displaced laterally by a pelvic mass, but there was no evidence of obstruction. Cystogram revealed moderate elevation of the bladder with nodular impressions along its floor, more on the left than on the right. (Fig. 1). There was considerable limitation of distensibility of the inferior portion of the bladder on the left, but no mucosal destruction or intraluminal filling defects could be demonstrated. Hemogram and blood chemistry determinations were all within normal limits. Biopsy of the mass revealed angiosarcoma. A course of supervoltage radiotherapy was given with marked reduction in the size of the mass and decrease of the edema of the left leg. Repeat cystogram, at the end of radiotherapy, revealed the bladder floor to be normal in position and the inferior contour of the bladder was now normally distensible with no residual nodular contour defects (Fig. 2).

DISCUSSION

Primary sarcoma of the prostate is a very uncommon disease entity with a reported ratio of one sarcoma to every thousand carcinomas of the prostatic gland (1). Although most authors agree that prostatic sarcomas affect children and young adults primarily (2, 3), in some large series the age range was equally



Case 208, Fig. 1. Cystogram reveals moderate elevation of the bladder with nodular impressions along the floor of the bladder, more on the left than on the right. There is considerable limitation of distensibility of the inferior portion of the bladder on the left but no mucosal destruction or intraluminal filling defects can be demonstrated.

Case 208, Fig. 2. Repeat cystogram at the end of radiotherapy reveals the bladder floor to be normal in position with normal distensibility of the inferior contour of the bladder and no residual nodular contour defects.

distributed from very young to very old (4). Some of the sarcomas have been diagnosed in infants as young as four months of age (3, 5). By 1950, only 225 cases of primary sarcoma of the prostate were published in the world literature. Primary angiosarcoma of the prostate was found in only one out of 38 cases of primary prostatic sarcomas described by Hillenbrand (6). It is often difficult to determine the exact site of origin of the sarcomas as they are usually quite extensive by the time they are first diagnosed. The primary site can be the prostate itself, the bladder floor, or the periprostatic tissues. The prognosis is universally bad with less than 5 per cent five year survival. Radiation therapy appears to be the treatment of choice. As in the case presented here, there is often a dramatic response in tumor size but recurrences and distant metastases are the rule.

Case Report: Angiosarcoma of the prostate.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Hans B. Schapira.

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The Urinary Excretion of the Neutral 17-Ketosteroids in Myotonic Dystrophy

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In previous studies of patients with myotonic dystrophy it was found that the basal urinary excretion of the neutral 17-ketosteroids is frequently reduced (1, 6–10). In addition, the adrenal cortical response to the exogenous administration of corticotropin is inadequate when the urinary titer of the neutral 17-ketosteroids is employed as an index. In an attempt to further delineate this abnormality, partition of the urinary neutral 17-ketosteroids has been carried out in the resting state and following the administration of corticotropin, dexamethasone, and human chorionic gonadotropin.

MATERIAL AND METHODS

Seven patients with myotonic dystrophy, 5 female and 2 male, were studied. In all, the basal urinary 24 hour titer of neutral 17-ketosteroids was measured and the neutral 17-ketosteroid content was partitioned on paper. In 5 of the 7, 4 female and 1 male, the urine was similarly analyzed following the administration of corticotropin, dexamethasone and human chorionic gonadotropin.

All urine specimens were collected for 24 hour periods, stored in the cold room and assayed within one week after collection. During the control and the experimental period, urines were collected separately for three successive days and the second day's collection was analyzed.

Corticotropin-gel was administered intramuscularly in a dosage of 40 units twice a day for two days in two subjects (F.R. and H.H.) and for six days in the remaining three patients. The 24 hour urine specimens collected on the last day were then analyzed.

Dexamethasone was administered by mouth in a dosage of 0.5 mg five times a day for five days to subjects F.R. and H.H. and the urine specimens collected on the fifth day were studied. In three additional patients, dexamethasone was given for seven days in the same amount and the 24 hour urine specimens collected on the seventh day were analyzed.

In five patients, human chorionic gonadotropin was given intramuscularly in a dosage of 5,000 I.U. once a day for two days. The second 24 hour urine collection was used for study.

From the Endocrine Research Laboratory of the Department of Medicine and the Department of Chemistry, The Mount Sinai Hospital, New York, N. Y. Aided by a grant from the Muscular Dystrophy Association.

* U. S. Public Health Service Training Grant Fellow.

Total Urinary Neutral 17-Ketosteroids: Two hundred ml of urine were boiled and hydrolyzed with 20 ml of hydrochloric acid for ten minutes. Extraction with ethyl ether, washing and purification procedures were carried out according to the method of Holtorff and Koch (2). The determination of total neutral 17-ketosteroids was based on this method employing the Zimmermann color reaction with dehydroepiandrosterone as a standard.

β-fraction: After determination of the total neutral 17-ketosteroids (17-KS), the total neutral fraction was employed for the separation of the β-ketonic fraction (consisting mainly of Δ^5-dehydroepiandrosterone) by the method of Frame (3). After separation of the β-fraction digitonide, the supernatant was employed for the measurement of the α-ketonic fraction. The difference between the total neutral 17-KS and α-ketonic fraction was taken to represent the β-fraction.

Chromatographic Separation of the 17-Ketosteroids: The paper partition chromatographic procedure for 17-ketosteroid fractionation was based on the method of Rubin *et al.* (4). This procedure was slightly modified in regard to the width of paper which varied from 4 to 7 cm depending upon the amount of 17-KS applied. The developing system was heptane saturated with propylene glycol at a temperature of 25°C. Individual pure standards of the ketosteroids assayed were chromatographed concurrently with the urine. Each zone was delineated by the Zimmermann reaction applied to a narrow strip cut out of the paper.

On the first paper chromatogram androsterone (including $\Delta^{9,11}$-androstene-3α-ol-17-one) and etiocholanolone (including $\Delta^{9,11}$-etiocholene-3αol-17-one) were separated and determined. The most polar zone was eluted and evaporated to dryness. This mixture of 11-oxygenated-17-ketosteroids was employed in the second paper chromatogram utilizing the same system for 72 hours. On the second paper chromatogram, androsterone-3α-ol-11,17-dione and etiocholane-3α-ol-11,17-dione were separated from an unresolved zone remaining close to the starting line. The latter zone was also determined by a color reaction and designated as the unresolved polar ketosteroids. It consists of a mixture of 11-hydroxylated compounds remaining unchanged during the course of acid hydrolysis and a group of unidentified compounds reacting positively to the Zimmermann color reaction.

RESULTS

In Table I and Fig. 1 are presented the data on six normal subjects. The findings in general, are similar to those reported by Jailer and his co-workers (5) in 21 normal subjects except that the β-fraction was lower in our subjects. However, values for the β-fraction determined by digitonin precipitation are usually less than when the assay is carried out by column chromatography.

The results in the subjects with myotonic dystrophy are presented in Table II and Figs. 3 to 8.

Basal Urinary 17-Ketosteroid Values in Subjects with Myotonic Dystrophy

The control urinary titers of the total neutral 17-ketosteroids are reduced as compared to the values obtained in normal subjects. This is reflected in the low absolute values for androsterone and etiocholanolone although in all instances

TABLE I

Urinary Neutral 17-Ketosteroids in Normal Subjects mg/24 hrs

Pt.	Age	Sex	Total 17-keto-steroids	Andro-sterone (A)	Etiochol-anolone (E)	11-Keto-andro-sterone	11-Keto-etiochol-anolone	Polar 17-KS	β-fraction %	A/E Ratio
A.S.	27	M	13.5	3.8	4.0	0.9	0.8	3.5	1.1	1.0
R.K.	24	M	8.4	2.3	3.3	0.3	0.3	1.5	7.2	0.7
E.H.	22	M	13.2	3.3	3.6	1.3	0.7	2.2	1.0	0.9
M.R.	27	F	9.9	2.1	3.3	0.4	0.5	1.5	8.4	0.6
J.R.	36	F	10.1	3.0	3.8	0.6	0.9	1.4	1.9	0.8
P.A.	22	F	7.5	2.2	1.8	0.5	0.7	0.7	9.3	1.2
			7.5	1.8	1.9	0.2	0.5	1.5	9.3	1.0

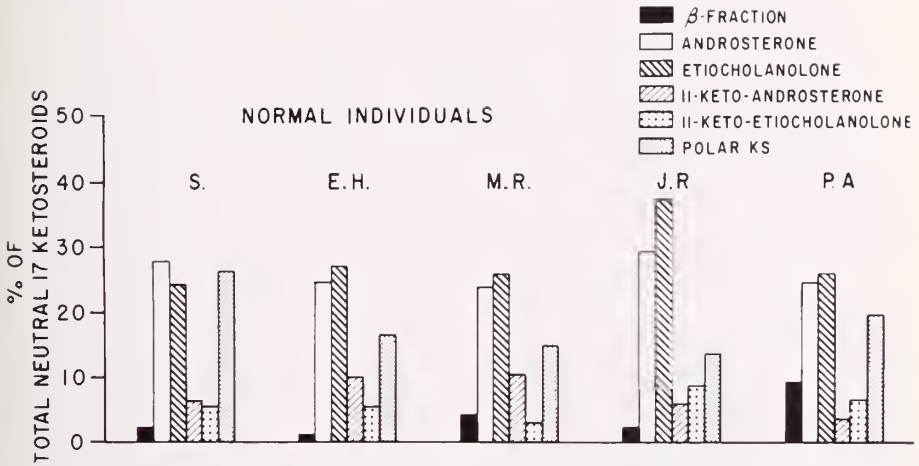

FIG. 1. Percentage of each of the component fractions of the urinary neutral 17-ketosteroids excreted in the basal state by 6 normal subjects.

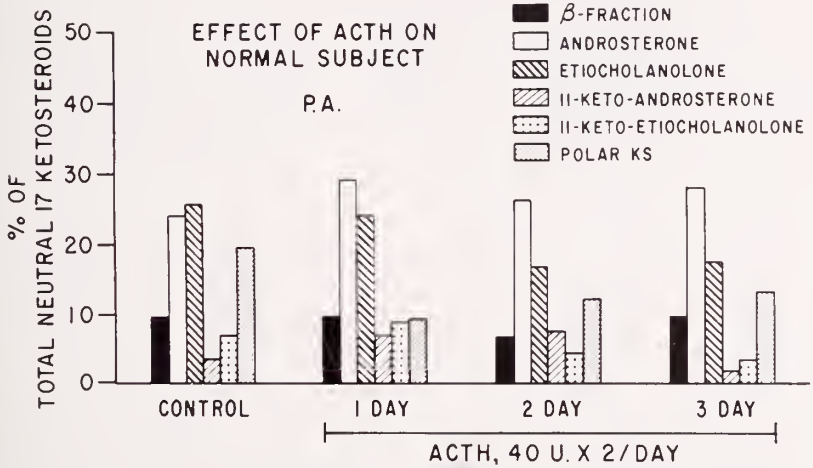

FIG. 2. Effect of corticotropin on the several fractions of the urinary neutral 17-ketosteroids in a normal subject.

with the exception of one subject (M.F.) the values are within the normal range reported by Jailer and his associates (5). The proportionate reduction in androsterone and etiocholanolone results in a normal A/E ratio. The levels of the 11-keto derivatives of androsterone and etiocholanolone as well as the unresolved polar ketosteroids are also somewhat reduced although the number of control subjects available for comparison is small.

TABLE II

Neutral 17-Ketosteroids in Patients with Myotonic Dystrophy mg/24 hrs

Age & Sex	No. days of therapy	Total neutral 17-KS	Androsterone (A)	Etiocholanolone (E)	11-Ketoandrosterone	11-Ketoetiocholanolone	Unresolved polar ketosteroids	β-fraction %	A/E Ratio
F.R.	Control	3.8	0.9	1.1	0.2	0.2	0.7	2.2	0.8
44	2 ACTH	6.3	2.0	1.1	0.6	0.5	1.0	15.0	1.8
F	5 Dexamethasone	2.2	0.6	0.4	0.1	0.2	0.2	14.4	1.5
	2 HCG	4.2	1.4	0.8	0.4	0.3	0.5	11.3	1.8
H.H.	Control	5.4	1.1	1.1	0.6	0.6	1.0	9.1	1.0
53	2 ACTH	13.4	3.7	1.7	1.8	2.0	2.1	14.2	2.2
F	5 Dexamethasone	4.7	1.1	0.8	0.4	0.3	0.6	13.6	1.4
	2 HCG	7.9	1.5	1.0	0.9	0.8	0.9	3.2	1.5
M.F.	Control	3.8	0.5	0.6	0.2	0.3	1.1	17.0	0.8
36	6 ACTH	11.1	3.2	2.3	1.3	0.4	1.7	13.9	1.4
F	7 Dexamethasone	3.5	0.6	0.6	0.2	0.1	1.1	12.5	1.0
	2 HCG	5.8	1.0	0.6	0.5	0.4	0.8	8.3	1.7
R.L.	Control	3.9	1.0	1.4	0.2	0.1	0.7	7.1	0.7
60	6 ACTH	13.9	4.7	2.9	0.2	0.9	2.9	5.3	1.6
F	7 Dexamethasone	2.4	0.9	0.3	0.2	0.2	0.4	6.1	3.0
	2 HCG	4.1	0.7	1.0	0.1	0.3	1.2	2.5	0.7
H.L.	Control	8.2	2.4	1.9	0.8	0.6	1.6	5.5	1.3
39	6 ACTH	18.6	5.4	3.8	1.5	1.5	1.6	2.6	1.4
M	7 Dexamethasone	8.7	2.7	1.4	0.5	0.5	0.9	10.9	1.3
	2 HCG	9.3	2.4	3.6	0.6	0.5	1.1	6.0	0.7
G.W.	Control	8.3	1.9	2.1	0.7	0.6	1.8	15.5	0.9
32									
F									
B.R.	Control	6.2	1.7	2.0	0.3	0.3	1.1	9.7	0.9
37									
M									

Effect of Corticotropin on the Urinary 17-Ketosteroid

Following the administration of corticotropin (Table II) there is a moderate increase in the urinary titers of the total neutral 17-ketosteroids as well as that of androsterone, etiocholanolone, 11-ketoandrosterone and 11-ketoetiocholano-

lone and the unresolved polar ketosteroids. The administration of corticotropin results in an increase in the A/E ratio and although the percentage of the β-fraction is not consistently altered the absolute quantity is augmented.

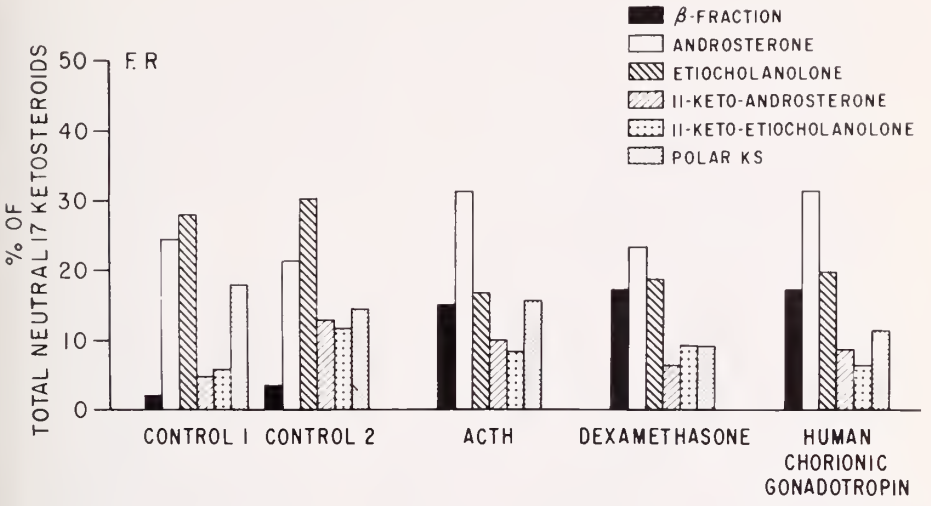

FIG. 3. Effect of corticotropin, dexamethasone and human chorionic gonadotropin on the urinary neutral 17-ketosteroids in a patient with muscular dystrophy (F.R.).

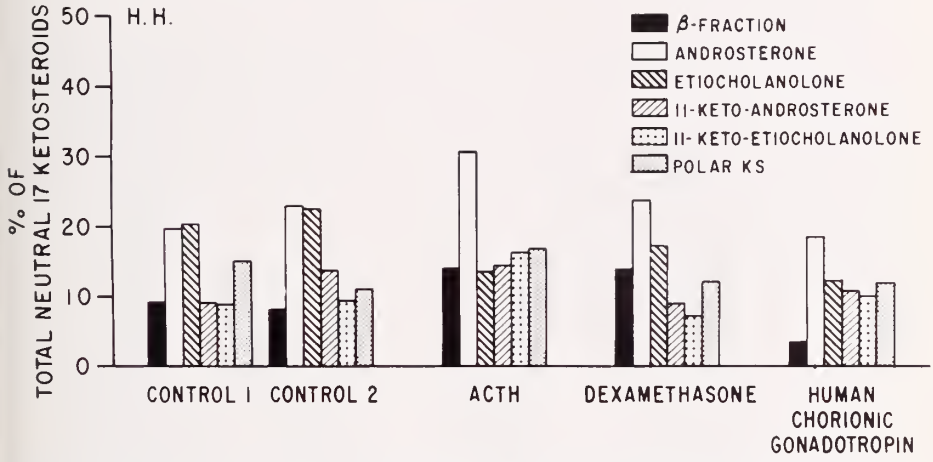

FIG. 4. Effect of corticotropin, dexamethasone and human chorionic gonadotropin on the urinary neutral 17-ketosteroids in a patient with muscular dystrophy (H.H.).

Effect of Dexamethasone

Some reduction in the urinary titer of the total neutral 17-ketosteroids as compared to the control values occurred in only 2 of 5 patients following the administration of dexamethasone (Table II). However, this may be due to the generally low titers encountered during the control period. In general, the urinary excretion of androsterone remained unaltered although there was some sugges-

tion that there was a decrease in the urinary titer of etiocholanolone. No definite effect was noted on the excretion of the 11-keto compounds. In 3 of 5 patients the A/E ratio exceeded that of the control period and tended to be intermediate between that of the control and corticotropin periods.

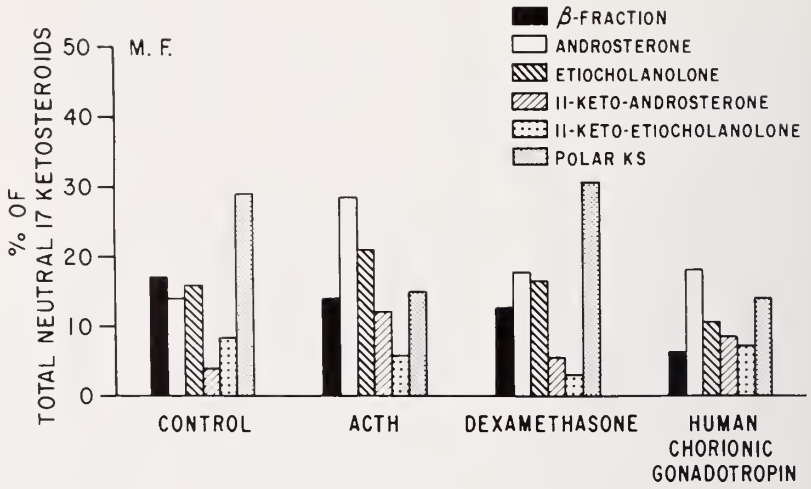

Fig. 5. Effect of corticotropin, dexamethasone and human chorionic gonadotropin on the urinary neutral 17-ketosteroids in a patient with muscular dystrophy (M.F.).

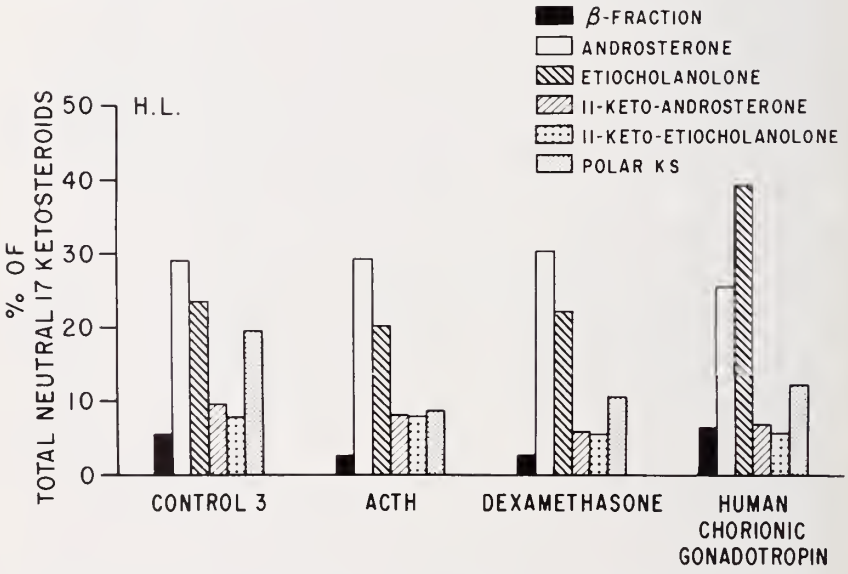

Fig. 6. Effect of corticotropin, dexamethasone and human chorionic gonadotropin on the urinary neutral 17-ketosteroids in a patient with muscular dystrophy (H.L.).

Effect of Chorionic Gonadotropin

The administration of human chorionic gonadotropin was essentially without effect on the titer of the total neutral 17-ketosteroids although in three subjects

there was some increase in the urinary excretion of androsterone and in the A/E ratio (Table II).

DISCUSSION

Paper chromatographic partition of the urinary neutral 17-ketosteroids in patients with myotonic dystrophy reveals a reduction in the titer of the total

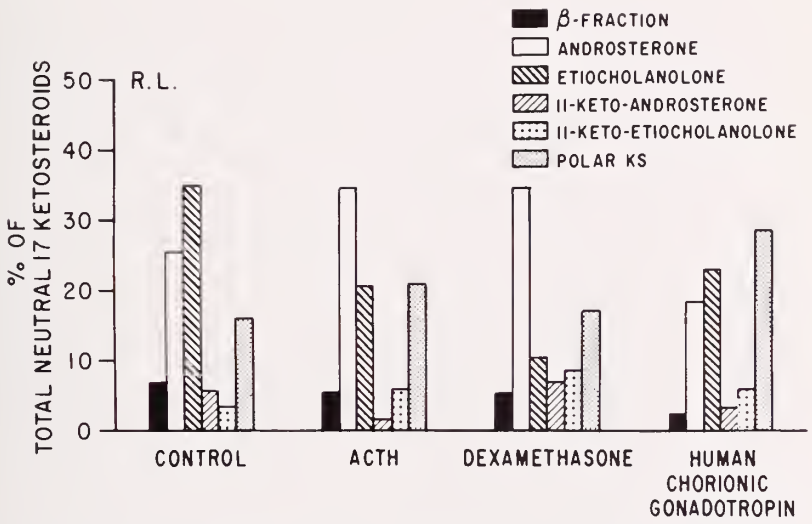

FIG. 7. Effect of corticotropin, dexamethasone and human chorionic gonadotropin on the urinary neutral 17-ketosteroids in a patient with muscular dystrophy (R.L.).

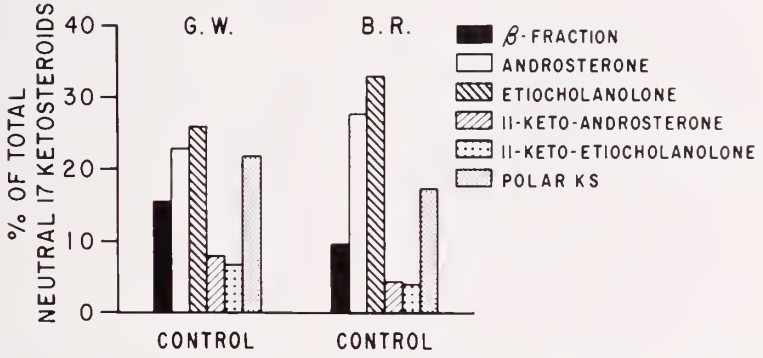

FIG. 8. Basal excretion of the urinary neutral 17-ketosteroids in 2 patients with myotonic dystrophy.

neutral 17-ketosteroids as well as a decrease in all the fractions. Although the testicular atrophy that occurs in male subjects with this disease contributes to the low urinary content of the neutral 17-ketosteroids, it is apparent from the reduced values found in women similarly affected and the decreased quantities of the 11-keto compounds observed in both sexes that the adrenal cortex is secreting decreased quantities of androgen. The low basal level of adrenocortical

function is further evidenced by the failure of dexamethasone to induce a constant and significant reduction in the urinary excretion of the neutral 17-ketosteroids.

Kappas and his associates studied the chromatographic separation of the urinary neutral 17-ketosteroids in two male patients with dystrophia myotonica (7). In both subjects, the urinary excretion of the C_{19}-11-oxysteroids was within the normal range, while that of the C_{19}-11-desoxysteroids was slightly reduced. In neither subject did the administration of corticotropin result in an increase in the urinary content of the C_{19}-11-desoxysteroids although in one a slight rise in the titer of the C_{19}-11-oxysteroids was observed. Chorionic gonadotropin was without effect on the C_{19}-11-oxysteroid output but its administration induced a slight increase in the quantities of the urinary C_{19}-11-desoxysteroids. The latter increase was presumably of testicular origin.

Kuhn and Staudinger also investigated the urinary excretion of the neutral 17-ketosteroids in myotonic dystrophy employing column chromatography following enzymic and acid hydrolysis (6). The fractions were divided into androstenedione and the nonpolar steroids, dehydroepiandrosterone, androsterone, etiocholanolone, and the more polar compounds. They reported that the absolute values for dehydroepiandrosterone (the β-fraction), androsterone, etiocholanolone, and the polar steroids were low although the percentages of these components were within the normal range. It should be noted that the percentage of the β-fraction determined by column chromatography is ordinarily higher than values obtained with digitonin precipitation.

Low basal urinary excretions of neutral 17-ketosteroids were also reported by Caughey and Brown (13), Martin and Patee (12), and Barris and Strassman (14). However, instances of myotonic dystrophy have been reported by Jacobson and his associates (9) and by Holland and Richardson (10) and others in whom normal values for the urinary content of neutral 17-ketosteroids were encountered. In addition, in these subjects, as well as those studied by Decourt and his co-workers (15) the titer of the urinary neutral 17-ketosteroids was increased when corticotropin was administered. In our subjects there also was a moderate increase in the total urinary neutral 17-ketosteroids and in the individual fractions following injections of corticotropin. Drucker and his associates reviewed the literature and studied 17 patients of their own, in 11 of whom the total urinary neutral 17-ketosteroids were measured (16). They found that in 73 per cent of 121 subjects reviewed the titer was subnormal.

The results obtained in this investigation shed no further light on the cause of the low basal urinary excretion of the neutral 17-ketosteroids in myotonic dystrophy. However, the studies in women demonstrate that diminished adrenocortical secretion plays a role and the experiments employing human chorionic gonadotropin in men reveal that there is frequently an impairment of testicular function as well. It is possible, that the low titers may in part reflect the chronicity of the illness and the marked muscle wasting found in patients with this disorder.

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The Urinary Excretion of Adrenal Corticoid Metabolites in Myotonic Dystrophy

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In previous studies from this and other laboratories it was found that the urinary excretion of the neutral 17-ketosteroids is frequently reduced in myotonic dystrophy (1, 2). This reflects decreased secretion by both the adrenal cortex and the testis. The various neutral 17-ketosteroid fractions all participate in the absolute decrease in titer but the relative proportion of each component is similar to that encountered in the normal subject. The administration of corticotropin is frequently only modestly effective in increasing the titer of the urinary neutral 17-ketosteroids. On the other hand, normal quantities of the glucogenic corticoids are usually found in the urine of patients with myotonia dystrophica and the titer often, although not invariably, increases following the administration of corticotropin (1, 3). In view of the disparity between the findings in respect to the urinary neutral 17-ketosteroids and the glucogenic corticoids, it was deemed of interest to study the urinary excretion of the glucogenic corticoids in patients with myotonic dystrophy both by the conventional chemical (Porter-Silber) method and by partition chromatography.

MATERIALS AND METHODS

Four patients, 1 male and 3 female, were studied. In all subjects, studies of the urinary excretion of the Porter-Silber chromogens (17-hydroxycorticoids), cortisone, cortisol (hydrocortisone), tetrahydrocortisone, tetrahydrocortisol and allotetrahydrocortisol were carried out in the basal state and following the administration of corticotropin, dexamethasone, and human chorionic gonadotropin.** All urine specimens were collected for 24 hour periods, stored in the cold room without preservative and analyzed.

Corticotropin-gel (ACTH) was administered intramuscularly in a dosage of 40 units twice a day for two days in one subject (H.H.) and for six days in the other subjects. The urine collection of the last day was analyzed.

Dexamethasone was administered by mouth in a dose of 0.5 mg five times a day for five days to patient H.H. and for seven days to the other subjects. The urine collected from H.H. on the fifth day of dexamethasone administration and

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** The following abbreviations are used. 4-Pregnen-17α,21-diol-3,11,20-trione: cortisone or Compound E; 4-Pregnen-11β,17α,21-triol-3,20-dione: cortisol or Compound F; 5β-Pregnan-3α,17α,21-triol-11,20-dione: tetrahydrocortisone or THE; 5β-Pregnan-3α,11β,17α,21-tetrol-20-one: tetrahydrocortisol or THF; 3α-Allotetrahydrocortisol: allo-THF; Corticotropin: ACTH; Human chorionic gonadotropin: HCG.

the urines collected from the other patients on the seventh day of therapy were analyzed.

In all patients, human chorionic gonadotropin (HCG) was given intramuscularly in a dosage of 5,000 I.U. once a day for two days. The urine collected on the second day of therapy was then studied.

Porter-Silber Reacting Material (17-hydroxycorticoids)

A one ml aliquot was analyzed by the Peterson modification of the Porter-Silber method for the determination of 17-hydroxycorticoids (4, 5).

Extraction and Purification of Corticoids

Half the volume of the 24 hour urine specimen, adjusted to pH 4.0, was incubated for 24 hours at 37°C with β-glucuronidase (Sigma Chemical Co.) 50 units/ml of urine. Extraction with chloroform, washing with 0.1 N-NaOH and further treatment were carried out by routine methods. The fractionation of the individual 17-OH corticosteroids was carried out by paper chromatography.

Separation and Determination of Individual 17-OH Corticoids

The first paper chromatogram for the separation of cortisone (E), cortisol (F) and more polar corticoids was run in the system of Zaffaroni-Burton (Toluene-propylene glycol) for 72 hours. The E and F zones were detected by ultraviolet scanning and the blue tetrazolium (BT) reaction on a narrow strip cut out of the paper. The site of each zone was identified by running 20μg each of the pure standard steroids simultaneously on the same paper. Each zone was then cut, eluted with chloroform-methanol (1:1), and evaporated to dryness under a stream of nitrogen. The residue was dissolved in absolute ethanol. An appropriate aliquot was developed by the Porter-Silber reaction and measured quantitatively in the Beckman spectrophotometer by comparison with samples of the pure steroid. The more polar steroid zone, located between the upper end of the cortisol zone and the starting line of the first paper chromatogram was detected by the blue tetrazolium reaction. The eluate of this polar steroid zone was placed on a second paper partition chromatogram which employed a benzene-formamide system and was allowed to run for 72 hours (6, 7). Twenty micrograms of tetrahydrocortisone (THE) and tetrahydrocortisol (THF) were always applied to adjacent strips as comparison standards. The eluate of the zone was applied to the third paper chromatogram in a chloroform-formamide system for 24 hours (8). In this system the THE and 3-α-allo-tetrahydro-cortisol (allo-THF) zones could be separated. The eluates of THF, allo-THF and THE and the second and third paper chromatogram were handled in the same fashion as the eluates of E and F obtained from the first paper chromatogram. Measurement was carried out by the Porter-Silber reaction utilizing a pure sample of each steroid for comparison.

RESULTS

Control Values

In the control specimens, the urinary titers of the Porter-Silber chromogens were within the low normal range or slightly subnormal. Urinary cortisone and

TABLE I

Glucocorticoid Excretion in Myotonia Dystrophica (per 24 hours)

Pt.	Sex and Age	No. of days of Rx.	17-OH-(Porter Silber) (mg)	Cortisone (μg)	Cortisol (μg)	THE (μg)	Allo-THF (μg)	THF (μg)	Ratio THF/THE
H.H.	F 53	Control	3.0	230	140	1100	360	400	0.4
		2 ACTH	7.9	360	290	4200	280	1500	0.3
		5 Dexamethasone	2.3	380	380	470	430	670	1.3
		2 HCG	2.3	140	130	800	340	160	0.2
M. F.	F 36	Control	2.8	210	460	820	470	260	0.3
		6 ACTH	11.4	280	2000	3800	310	550	0.2
		7 Dexamethasone	0.6	34	110	270	76	120	0.4
		2 HCG	2.0	28	64	610	91	220	0.3
H. L.	M 39	Control	1.7	130	100	1000	100	270	0.2
		6 ACTH	6.1	220	280	3200	380	990	0.3
		7 Dexamethasone	0.6	62	53	170	99	79	0.5
		2 HCG	2.7	91	140	650	280	380	0.6
R. L.	F 60	Control	2.7	230	190	1000	530	880	0.8
		6 ACTH	11.1	660	460	4100	1600	3000	0.8
		7 Dexamethasone	0.6	80	130	220	120	98	0.5
		2 HCG	1.2	65	45	190	100	160	0.8
Normal Women (22–38 yrs) (6–8)			2.6–6.0			1700–3500	100–700	300–900	
Normal Men (18–35 yrs) (8–10)			4.5–7.9			1800–5300	200–1200	600–1400	
Normal Subjects (7 Male 2 (Female (9)				60–135	40–100	1280–2800	440	320–960	
10 "Healthy" Men (20)				20–200	10–80				
10 Normal Men (21)				20–400	41–212	840–2870		220–1200	
(10)						710–5600	110–2100	920–3400	

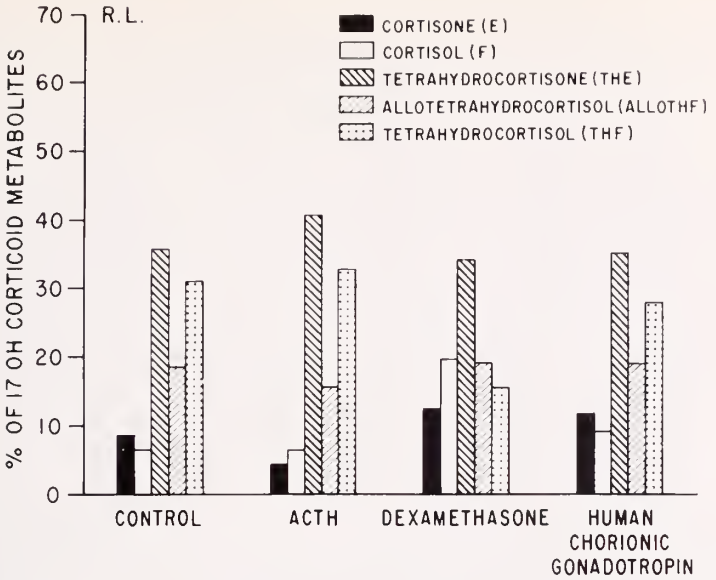

FIG. 1. Percentage of the various corticoid metabolites excreted before and following the administration of corticotropin, dexamethasone and human chorionic gonadotropin to a patient with myotonic dystrophy (R.L.).

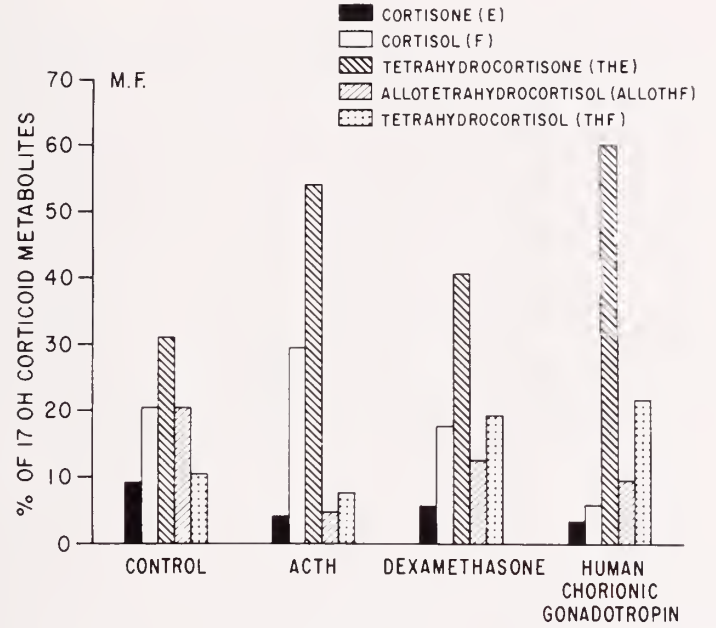

FIG. 2. Percentage of the various corticoid metabolites excreted before and following the administration of corticotropin, dexamethasone and human chorionic gonadotropin to a patient with myotonic dystrophy (M.F.).

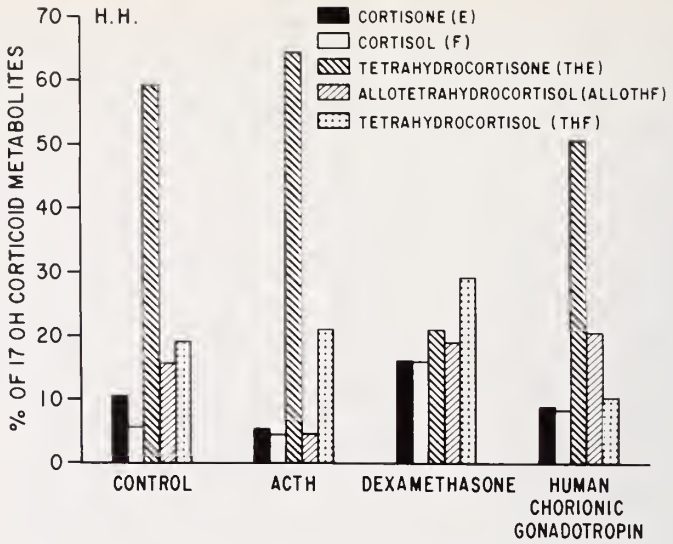

FIG. 3. Percentage of the various corticoid metabolites excreted before and following the administration of corticotropin, dexamethasone and human chorionic gonadotropin to a patient with myotonic dystrophy (H.H.).

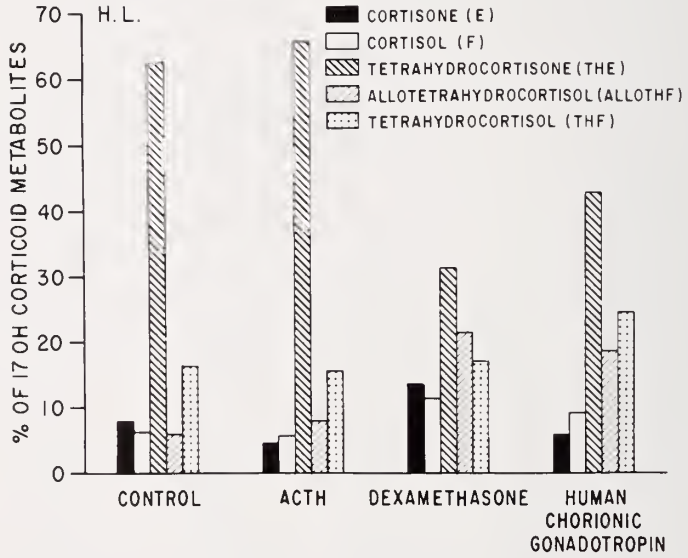

FIG. 4. Percentage of the various corticoid metabolites excreted before and following the administration of corticotropin, dexamethasone and human chorionic gonadotropin to a patient with myotonic dystrophy (H.L.).

cortisol ranged from 130 to 230 and 100 to 460 μg/24 hours respectively compared to the normal values of 60 to 135 for E and 40 to 100 for F, given by Cost (9). Both the values for THE excretion, which were 820 to 1080 μg/24 hours and the values for THF were on the low side, whereas the titers of allo-THF were

within the normal range. However, because of the small number of data on normal subjects available in the literature, comparison to normal values is difficult.

Effect of Corticotropin

The administration of corticotropin induced only a very moderate rise in the urinary titer of the Porter-Silber chromogens, the maximum value attained being 11.4 mg/24 hours. Rises were induced in all the fractions studied in all subjects except for the excretion of allo-THF which decreased in two subjects (H.H. and M.F.). In general, the most striking absolute increases were noted in the THE fraction. However, the ratio of tetrahydro F/tetrahydro E is not consistently altered in contrast to the increase reported in normal subjects treated with corticotropin by Gold and his associates (10).

Effect of Dexamethasone

Dexamethasone induced a fall in the Porter-Silber chromogens and of the glucocorticoid steroid fractions in three of the four patients. This was particularly noted in the excretion of tetrahydro E. In the fourth subject (H.H.) treated for only five days no significant fall in the Porter-Silber chromogens nor of the steroid fractions was noted except for THE.

Effect of Chorionic Gonadotropin

The alterations observed following treatment with chorionic gonadotropin were quite variable. The Porter-Silber chromogen titer remained unaltered in three of the subjects and fell in one patient (R.L.). In the last, the titers of all fractions were reduced. In the other three subjects, the titers of cortisone and cortisol fell in one (M.F.); THF decreased in one subject (L.H.); allo-THF fell in one (M.F.) and rose in one (H.L.); and THF was lower in one patient (H.H.). The other values remained essentially unaltered.

DISCUSSION

The current data demonstrate low or low normal basal levels of 17-hydroxycorticoids in subjects with myotonic dystrophy and an impaired responsiveness of the adrenal cortex to the administration of corticotropin when the Porter-Silber chromogen content of the urine is used as an index. In our previous studies on three subjects, one of whom was again studied in this investigation (H.H.), a low basal level of the formaldehydrogenic corticoids and impaired responsiveness to corticotropin was noted in one whereas the other two subjects behaved in a normal fashion (1). Low values for the urinary titers of the 17-hydroxycorticoids in patients with this disorder were also reported by Becker and his associates (11) in two patients, and by Jacobson and his collaborators (3) in three of four subjects. In the two patients given ACTH by these latter investigators only a modest increase in the titer of the adrenal corticoids was induced.

On the other hand, normal basal levels of the total 17-hydroxycorticoids (by

the method of Appleby *et al.* (12)) were reported for two patients by Marshall (13), and Ledwith and Whipple (14) reported a high titer in one subject after corticotropin administration (22mg/24 hrs) although the basal level was not determined. Holland and Hill reported low normal basal values in two patients but a normal ACTH response in one of the subjects (15). In a study of 17 patients with this disorder coupled with a review of the literature, Drucker and his associates found that 21 of 25 patients with this disorder had normal urinary corticoids (16). In their experience, only one of four had a low urinary 17-hydroxycorticoid titer and the urinary excretion of the 17-ketogenic steroids was normal in 10 of 11 subjects. When they tested the response of the plasma 17-hydroxycorticoids to the administration of corticotropin they found it to be normal in 10 of 12 patients. These latter investigators believe that the inadequate responses to ACTH reported in the literature may have resulted from inactivation of the corticotropin which had been administered intramuscularly.

Our data demonstrate that the 17-hydroxycorticoids in the urine are not consistently altered following the administration of chorionic gonadotropin. Hill and his associates found similar results in normal subjects and in a patient with myotonic dystrophy (17, 18).

It is possible that the reduction in the basal excretion of the glucocorticoids may reflect the reduction in muscle mass. Romanoff and her associates have demonstrated a higher adrenal output of cortisol in young as compared to old subjects, but find no difference when it is expressed in relation to muscle mass as evidenced by creatinine output (6–8).

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A Study of Subarachnoid Hemorrhage and Intracranial Aneurysm

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The widespread interest in the problem of intracranial aneurysm and subarachnoid hemorrhage reflects the lack of clear-cut answers for clinical management. This paper is limited to three different aspects of the many problems: 1) the management of non-bleeding intracranial aneurysm; 2) subarachnoid hemorrhage due to ruptured intracranial aneurysm; 3) subarachnoid hemorrhage of unknown cause. Neurosurgical opinions vary from "early intracranial surgery for aneurysms of the circle of Willis or its branches, preferably within six days after presenting symptoms, whenever age and condition of patient permit" (1), to "there is no proof that surgical treatment of ruptured intracranial aneurysms has effectively lowered the mortality unless a large hematoma is present and can be evacuated" (2). The mortality rate of subarachnoid hemorrhage due to ruptured aneurysm treated conservatively is reported as 50 per cent within the first two months (⅔ of the patients dying of an initial hemorrhage and ⅓ of a recurrent hemorrhage) and another 20 per cent of the remaining patients predicted to die within one year (3). However, in subarachnoid hemorrhage of undetermined cause, the mortality rate has been reported at 5%, 14%, and as high as 27%, and the prognosis for these patients is considered excellent if the patient lives past the first year (4–6). Some clinicians question the above gross figures, "excluding those patients who terminate fatally in the early danger period, conservatively treated and surgically treated aneurysms have approximately the same prognosis" (7). Graff states that the mortality of intracranial attack on an aneurysm within the first two to three weeks after the hemorrhage is as great as leaving the patient untreated (8).

The following cases were collected over a six year period from 1953–1958. It is hoped that an analysis of the material will serve as a control group for a current study in which patients who have had subarachnoid hemorrhage are being treated with hypotensive techniques.

The clinical factors which are considered most important for determination of management seem to be: 1) presence or absence of an aneurysm; 2) patient's age; 3) duration of acute episode of bleeding from onset of symptoms; 4) patient's clinical status, which has been delineated as follows: stage I—without hemorrhage; stage II—intracranial hemorrhage without neurological signs; stage III—intracranial hemorrhage, neurological signs, but no marked disturbance of consciousness or sensorium; stage IV—intracranial hemorrhage, diminished level of consciousness and/or a severe organic mental syndrome.

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MATERIAL

There were 125 patients in this study. Table I describes the three major groups and tabulates whether they were treated surgically or conservatively, and whether or not they died during hospitalization. Ninety-nine patients (50 with aneurysms and 49 without proved aneurysms) were managed conservatively. This reflects the attitude of the attending neurologists at this hospital and the fact that most patients with neurological illnesses are admitted to a neurological rather than a neurosurgical service. Table II describes the patients in terms of the presence of an aneurysm, patients' ages, and the clinical course (SL—surgically

TABLE I

Total Number of Patients—125

	No. of Cases	
Group I—Intracranial Aneurysm without Hemorrhage		7 Cases
A. Surgically treated	3	
I. Died during hospitalization	1	
II. Alive after hospitalization	2	
B. Conservatively treated	4	
I. Died during hospitalization	0	
II. Alive after hospitalization	4	
Group II—Subarachnoid Hemorrhage Due to Ruptured Intracranial Aneurysm		65 Cases
A. Surgically treated	19	
I. Died during hospitalization	4	
II. Alive after hospitalization	15	
B. Conservatively treated	46	
I. Died during hospitalization	20	
II. Well after hospitalization	26	
Group III—Subarachnoid Hemorrhage of Unknown Cause		53 Cases
A. Surgically treated	4	
I. Died during hospitalization	2	
II. Well after hospitalization	2	
B. Conservatively treated	49	
I. Died during hospitalization	14	
II. Well after hospitalization	35	

treated and alive; SD—surgically treated and died; CD—conservatively treated and died; CL—conservatively treated and alive). It is noteworthy that a predominant number of the patients in this study fall in the older age group—65 patients over 50 years of age, 34 patients in the fourth decade of life. In terms of over-all mortality among patients with aneurysms, 25 of 72 died during the acute illness, attesting to the gravity of this illness.

Since the diagnosis of an aneurysm is based on angiography, some very critical questions arise. Ideally, any patient with either subarachnoid hemorrhage or neurologic involvement such as a cranial nerve palsy, which is discovered due to an aneurysm, ought to have complete intracranial angiography, namely, bilateral carotid artery and vertebral-basilar artery study. This ideal is not attained in many cases for various reasons, such as: denial of consent for angiog-

raphy, the procedure was attempted but was unsuccessful, the patient was considered too ill for a complete study, the family was not willing to consent to additional procedures after being told that an aneurysm had been found with the initial angiogram, the referring internist, fearing angiographic complications, disagreeing with the neurologist's recommendations for complete angiography, an attending neurologist thinking, especially with reference to vertebral-basilar circulation, that the morbidity of this latter procedure inasmuch as the posterior circulation is almost inaccessible for surgery outweighed any practical benefit for the patient. However, with respect to these problems, the teaching at this institution has emphasized the importance of obtaining as much clinical information as possible. As time has gone on, most patients have had total angiography. Currently, the potential morbidity (9, 10) of the procedure is not a major factor in determining the indication for the procedure. Clinical judgment for per-

TABLE II

Patient's Age at Time of Hospitalization and Clinical Course

Age	Patients with aneurysm					Patients without aneurysm				
	18–29	30–39	40–49	Over 50	Total	18–29	30–39	40–49	Over 50	Total
SL (19)	1	4	2	10	17	1	0	0	1	2
SD (7)	0	0	2	3	5	1	0	1	0	2
CD (34)	2	3	5	10	20	0	1	7	6	14
CL (65)	2	6	7	15	30	4	1	10	20	35
Total (125)	5	13	16	38	72	6	2	18	27	53

SL—Surgically treated and alive after hospitalization.
SD—Surgically treated and died during hospitalization.
CD—Conservatively treated and died during hospitalization.
CL—Conservatively treated and alive after hospitalization.

forming angiography is based on the patient's clinical condition and the need to obtain as much information as possible for management and prognosis.

Table III summarizes the experiences in terms of the diagnostic procedures, with reference to their ultimate clinical course and their clinical state during hospitalization. Other than giving a general perspective, this indicates that the very ill patients had relatively fewer procedures performed; 27 of them had no procedures done, 21 only had one procedure performed. But, countrariwise, 8 of the 9 patients with complete studies were also in a critical state. Actually, what is not demonstrated is that as the experience of the neurologists increased, more and more patients have had more complete studies. In the past two years, with the use of brachial catheterization to obtain visualization of the vertebral-basilar circulation, almost all patients have had total angiography.

Table IV lists the patients who had known hypertension and demonstrates how many of them had intracranial aneurysms. This emphasizes that hypertension per se is perhaps not a major cause of intracranial bleeding. Theoretically, hypertension may contribute to the weakening of the aneurysm wall in those patients who, unfortunately, have such pathology. When patients who are known

to be hypertensive have intracranial bleeding, it is too often assumed that this is a natural consequence of their hypertension. This thought should be reconsidered in view of the incidence of intracranial aneurysms.

The location of the majority of the intracranial aneurysms in this study was on the carotid artery (infraclinoid—19 and supraclinoid—16) (Table V). Over half of these patients, 38 of 72, were above the age of fifty, and this weighted the management towards conservative therapy. Also, 11 patients had multiple aneu-

TABLE III

Results of Angiography

	No Procedure	One Carotid	Both Carotids	Both Carotids Vertebral	One Carotid Vertebral
SL (19)	1	5	12	0	1
SD (7)	4	1	2	0	0
CD (34)	19	10	4	0	1
CL (65)	14	21	20	9	1
Total (125)	38	37	38	9	3
Stage I (22)	4	6	9	0	3
Stage II (10)	2	3	5	0	0
Stage III (20)	5	7	7	1	0
Stage IV (73)	27	21	17	8	0
Total (125)	38	37	38	9	3

Number of possible procedures $125 \times 3 = 375$
Number of successful procedures $= 147$
Procedures not done $= 228$

TABLE IV

Patients with Hypertension

	With Aneurysm (Total—72)	Without Aneurysm (Total—54)
SL (19)	2	0
SD (7)	2	0
CD (34)	5	7*
CL (65)	9	10
Total	18	17

* No post mortem—5 patients.

rysms, a factor which also tended to rule out surgical intervention. One such patient was operated upon and others have been reported (11, 12) as being treated surgically.

The following two comments may be made about the patients who were not operated upon.

Sixty-five conservatively treated patients are alive; only one of the 30 who had a proved aneurysm has had a recurrent episode of bleeding since hospitalization. Two patients of 35 without proved aneurysms had recurrent hemorrhage, one of whom was a severe hypertensive and died in coma, probably of intracranial hemorrhage, but no autopsy was performed.

Thirty-four patients conservatively treated died; 20 had proved aneurysms and 8 of them had had a previous hemorrhage. Of 14 patients who had no aneurysm demonstrated, 4 died of recurrent bleeding.

The incidence of recurrent hemorrhage and the survival time of patients treated conservatively or by surgery cannot be translated into numbers. Rather than deal with statistics, it is more informative to give concise, but detailed information about these critically ill patients. Actually, this study is much too small to permit a definite statistical conclusion.

Group I. Intracranial Aneurysm Without Hemorrhage—Seven Cases

A. Three cases treated surgically

1. H.B. is a 38 year old man, who had a three week history of pain behind the right eye and double vision. The neurological examination revealed a third nerve palsy. The cerebrospinal fluid was normal. Two days after admission, a right carotid angiogram revealed an aneurysm at the junction of the internal carotid artery and the posterior communicating artery. A left carotid angiogram was normal. Two weeks later, a right common carotid ligation was performed without complication. The patient has done well 48 months after surgery.

TABLE V

Location of Aneurysm

	ICic	ICsc	ACo	ACe	MCe	PCe	PCo	Ve-Ba	Multiple
SL (17)									
Under 50	1	2	0	2	3	0	0	0	1
Over 50	6	0	1	2	1	0	0	0	0
SD (5)									
Under 50	0	0	0	1	0	0	0	1	0
Over 50	1	0	0	0	1	0	1	0	0
CD (20)									
Under 50	0	2	1	5	5	0	1	0	4
Over 50	0	2	2	1	4	0	0	1	0
CL (30)									
Under 50	5	5	4	0	3	0	2	1	4
Over 50	6	5	3	3	4	0	0	0	5
Total (72)	19	16	11	14	21	0	4	3	11*

* 3 patients had 3 aneurysms each.

2. T.M. was a 47 year old man, who had been hospitalized because of progressive neurological findings and symptoms pointing to brain stem disease. Spinal fluid revealed a protein of 120 mg% under normal pressure. The possibility of a space-occupying lesion was considered, but the patient refused procedures and was discharged. He was re-admitted three weeks later to the Neurosurgery Service because of progressive symptoms. A craniotomy was performed. During surgery, some bleeding resulted in the need to ligate one of the vertebral arteries. The patient did not recover from the operation. A postmortem examination revealed a large aneurysm at the origin of the basilar artery.

3. I.S. is a 57 year old woman, who was admitted because of pain on the left side of her face, drooping of the left eyelid, and double vision. The neurological examination revealed a left third nerve palsy and a questionable fifth nerve hypesthesia. The cerebrospinal fluid was normal. A left carotid angiogram revealed a large infraclinoid aneurysm of the internal

carotid artery. The left common carotid artery was ligated and some transient loss of vision followed this procedure. Her pain was considerably diminished and, twenty months later, she felt satisfied as far as the pain was concerned. The third nerve weakness is still present.

B. Four cases treated without surgery

1. F.O. is a 35 year old man, who complained of double vision in the horizontal plane of seven days' duration and drooping of the right lid. The neurological examination revealed a third and fourth nerve palsy and an hypesthesia in the ophthalmic division of the trigeminal nerve. Cerebrospinal fluid was normal. A right carotid angiogram revealed an aneurysm of the posterior communicating artery. A left carotid angiogram was normal. The patient refused vertebral angiography. Surgery was recommended, but the patient refused. There has been no change 14 months following discharge.

2. C.R. a 39 year old hypertensive woman, suffered head pain and weakness of the right hand two days prior to hospitalization. At the time of admission, there was a right hemiparesis and a right homonymous field defect. Cerebrospinal fluid was clear; the protein was 83 mg%. A left carotid angiogram was normal. A vertebral angiogram demonstrated a basilar artery aneurysm at its bifurcation into the posterior cerebral arteries. She was discharged and was well 32 months later.

3. S.M. is a 54 year old hypertensive man, who, for one month, suffered from drooping of the left eyelid and numbness of the left side of the face. The neurological examination revealed involvement of the third, fourth, fifth and sixth cranial nerves on the left side. The cerebrospinal fluid was normal. A left carotid angiogram revealed a large infraclinoid internal carotid artery aneurysm. A right carotid angiogram was normal. The patient was discharged and, 28 months later, is still well.

4. S.D. is a 75 year old hypertensive woman, who developed pain and closure of the right eyelid eleven days prior to admission. She had a right third nerve palsy. The cerebrospinal fluid was normal. A right carotid angiogram revealed a large aneurysm of the internal carotid artery. She was discharged and has been well 46 months after discharge.

The question may be raised that the patients with pain about the eye may have had slight bleeding and that the lumbar puncture did not reveal this because it was performed after absorption of blood from the subarachnoid space. However, it is known that many patients, including those suffering from diabetes mellitus, who develop extraocular pathology involving the third, fourth and sixth cranial nerves, suffer from pain. This pain usually is in the eye or above, and lateral to the orbit. Investigations of such cases during the acute episodes do not reveal subarachnoid hemorrhage. As a result, it has been preferable to include these patients as not suffering from subarachnoid hemorrhage.

Three of the patients (I.S., S.M., S.D.) had extremely large internal carotid aneurysms. It seems most likely that the pathology was present for a relatively long period of time, inasmuch as they were all over fifty years of age, and, actually, one patient was 75 years of age. Historically, none of these patients had ever bled intracranially.

The fact that a basilar artery aneurysm can present as a mass is not too frequently stressed. The patient who refused all procedures would most likely have had a pneumoencephalogram. However, it is evident that the neurologist must consider angiography, even when mass lesions are found in the posterior fossa by air study. Although posterior fossa aneurysms are rarely operated upon, some have been reported to have done well (13, 14). The other patient with a basilar artery aneurysm was also confusing. He clinically presented as a so-called "stroke." The elevated cerebrospinal fluid was suspicious of a mass

lesion. A normal left carotid angiogram was not expected, inasmuch as the clinical findings are usually seen in the distribution of the middle cerebral artery. The actual diagnosis only emphasizes how difficult these problems can be.

The fact that a 75 year old woman can finally develop symptoms due to an aneurysm which most likely has been present all her life is also deserving of comment. The natural history of such intracranial aneurysms is still unknown, but, obviously, they can be present for many years prior to producing symptoms.

Group II. Subarachnoid Hemorrhage due to Ruptured Intracranial Aneurysm

A. Surgically treated patients—Nineteen Cases

It is thought that a tabulation of these patients will not give as clear a picture as a relatively complete description of their clinical course. Consequently, they are described in somewhat greater detail.

Four patients died shortly after surgery.

1. B.M., a 45 year old hypertensive man, apparently had had two episodes of severe head pain, the first two years prior and the second one month before the present illness. Two weeks prior to admission, he had a sudden attack of severe vertigo, which necessitated hospitalization elsewhere. A spinal tap revealed bloody fluid and bilateral angiography revealed an aneurysm of the right anterior cerebral artery. He was admitted to this hospital for surgery and, on admission, there was a right sixth nerve palsy and a questionable right third nerve palsy. The optic discs were blurred. Two days later, a craniotomy was performed and an attempt was made to clip the aneurysm. In doing so, the wall of a blood vessel was cut. There was profuse bleeding and, although this was controlled, the patient did not recover from surgery and died the following day. A postmortem revealed an aneurysm of the right cerebral artery, at the junction of the internal carotid artery.

2. C.B. was a 52 year old hypertensive woman, who was rendered unconscious a week prior to admission. At that time, a lumbar puncture revealed bloody fluid. She was admitted to this hospital in coma, with right-sided neurological findings. A craniotomy was performed the day after admission, when she was in very poor condition, in an attempt to evacuate a possible intracerebral hematoma. This was not discovered and the patient expired two days later. Postmortem revealed rupture of an aneurysm of the left middle cerebral artery.

3. M.G., a 51 year old man, was admitted because of headache and a stiff neck of four days' duration. On examination, he also had a ptosis of the right eyelid. Right carotid angiogram revealed an aneurysm of the right internal carotid artery. A Silverstone clamp was placed on the right common carotid artery and the patient became hemiplegic. The clamp was loosened, but he did poorly. He had a gradual progressive downhill course, dying a few weeks after surgery. Postmortem revealed that unfortunately, the left internal carotid artery had been spontaneously thrombosed and, apparently, the cerebral circulation was irreparably damaged by ligature of the right carotid artery.

4. D.W., a 52 year old woman, suffered a sudden attack of severe head pain with a stiff neck a month before admission. On examination at that time, a bruit was heard behind the right ear and a spinal tap revealed xanthochromic fluid. Two weeks later, she was transferred to this hospital. Bilateral carotid angiography was performed and an aneurysm of the right posterior communicating artery was noted, at its junction with the carotid artery. A week later, she had another episode of severe head pain and a spinal tap revealed bloody spinal fluid. Two days later, a Silverstone clamp was placed on the right common carotid artery. She then developed a right hemiparesis, did poorly, and died two days later.

The following fifteen patients survived the surgical procedures.

1. M.S., a 47 year old woman, developed sudden head pain and confusion two weeks prior to admission. On admission, she was comatose, with left-sided neurological findings.

A spinal tap revealed bloody fluid. A right carotid angiogram the day after admission demonstrated a possible temporal lobe mass and a questionable aneurysm of the right cerebral artery. A craniotomy with decompression was performed. She did relatively well. One month after surgery, a pneumoencephalogram was performed, which revealed a dilated right ventricular system. Two weeks thereafter, a right carotid angiogram revealed an aneurysm of the right anterior cerebral artery. Three days later, a normal left carotid angiogram was demonstrated. Consequently, a craniotomy was performed and the aneurysm was packed. After a relatively stormy postoperative course, she did well. She was readmitted ten months later and, at that time, she only had a mild hemiparesis. A right carotid angiogram was repeated and it revealed the exact same aneurysm. Over the next two years, she had three admissions, the first because of convulsions, the second for a cranioplasty, and the third for a convulsion, at which time a vertebral angiogram was performed, which was normal. Fifty-five months since her first admission, she is doing relatively well.

2. C.C., a 27 year old woman, had had a previous hospitalization three months before admission because of severe head pain and a stiff neck. A spinal tap then revealed bloody fluid. Bilateral carotid angiography revealed an aneurysm of the right supraclinoid portion of the internal carotid artery. The right common carotid artery was ligated. Nine days after this, a craniotomy was performed and a clip was placed on the aneurysm at its origin. On admission to this institution, she had a mild organic mental syndrome and a left hemimotor-sensory syndrome. Spinal fluid was clear; the protein was 40 mg%. Repeat carotid angiography revealed a normal left carotid circulation and the right carotid angiogram revealed the hypaque passing through the clip, visualizing the aneurysm. She has done relatively well twenty-six months later.

3. C.M., a hypertensive 42 year old man, was admitted because of an episode of unconsciousness preceded by head pain. On examination, he had a stiff neck, an organic mental syndrome, and left hemimotor-sensory findings. The spinal fluid was bloody. Bilateral carotid angiography revealed an aneurysm of the left anterior cerebral artery at its junction with the internal carotid artery. Eleven days after these procedures, a Silverstone clamp was put on the common carotid artery and he has done relatively well for 61 months.

4. L.G., a 38 year old woman, was admitted with a two week story of confusion, lethargy, and left-sided weakness. On admission, she was semi-comatose and had a stiff neck. The cerebrospinal fluid was xanthochromic under a pressure of 230 mm. The next day, a right carotid angiogram revealed an aneurysm at the origin of the middle cerebral artery. There was a transient left hemiparesis following the angiogram. Three days later, a left carotid angiogram revealed an aneurysm at the bifurcation of the internal carotid artery. On that day, the right common carotid artery was ligated. Two days later, she became comatose and a right third nerve palsy was noted. A spinal tap performed the following day revealed xanthochromic spinal fluid. A craniotomy was performed and a subdural hematoma was evacuated over the right cerebral hemisphere. Although her clinical state eventually stabilized, she was left with marked neurological deficits, including a quadriparesis.

5. J.O., a 33 year old man, was hospitalized elsewhere one week before admission. At that time, he had severe head pain, lethargy and a stiff neck. Cerebrospinal fluid was bloody and a right carotid angiogram revealed an aneurysm of the left middle cerebral artery. The left carotid angiogram was normal. When transferred to this hospital, he only had a slight right facial asymmetry. He underwent a craniotomy and the aneurysm was clipped and packed with muscle. He has done well for twelve months following surgery.

6. G.B., a 37 year old man, a year previously had an episode of severe head pain. At that time, lumbar puncture revealed bloody fluid. Six days before admission, he again had head pain with lethargy. Upon hospitalization, there was slight weakness of the right extremities. A lumbar puncture revealed xanthochromic fluid. A left carotid angiogram was normal. A craniotomy was performed eight days later and the aneurysm was clipped. Following this, he developed a right hemiparesis and aphasia. There was gradual improvement. Prior to discharge, a left carotid angiogram was reported, which was normal. Follow-up nineteen months later revealed a slight aphasia and a mild hemiparesis. He was working part-time.

7. F.V., was 63 years of age. Seven years prior to hospitalization, he had an attack of severe

head pain during sexual intercourse and, approximately six months thereafter, developed progressive loss of vision in the left eye. During the past year, his vision began to be impaired in the right eye. On admission, he was blind in the left eye and could only see finger movements with the right eye. There was bilateral optic atrophy and also diminished smell bilaterally. A left carotid angiogram was unsuccessful. There was no filling of the vascular tree. A pneumoencephalogram revealed a mass in the frontal region. Six days later, he fell, striking his head, and developed an organic mental syndrome. Three days subsequently, a craniotomy was performed and a mass was noted in the subfrontal region. A needle was inserted into the mass and blood was obtained. Three weeks later, a left carotid angiogram revealed an aneurysm of the anterior cerebral artery and, three weeks later, a right carotid angiogram revealed filling of the same aneurysm from the right side. A Silverstone clamp was placed on the left common carotid artery. However, an infection developed at the operative site and the clamp was extruded. He did very well and was discharged. Three months later, he developed jaundice. Unfortunately, at the time of abdominal surgery, cardiac arrest ensued and he died.

8. S.R., a 60 year old man, developed pain over the left eye two weeks prior to admission. He also saw double. On admission, he had a left third nerve palsy. Lumbar puncture revealed bloody fluid. A left carotid angiogram demonstrated an aneurysm of the infraclinoid part of the internal carotid artery. A right carotid angiogram was normal. Sixteen days later, a Silverstone clamp was applied to the left common carotid artery. There was very little improvement of the third nerve lesion. Four months later, the clamp was removed. He has done relatively well during the past six years.

9. B.W., a 53 year old woman, developed severe head pain behind the left eye two weeks prior to admission. At hospitalization, she had a stiff neck and the left palpebral fissure was smaller than the right. Lumbar puncture revealed xanthochromic fluid. She did relatively well and was discharged, only to be re-admitted three weeks later because of severe head pain and ptosis of the right eyelid. A right carotid angiogram demonstrated an aneurysm of the internal carotid artery; a left carotid angiogram was normal. Two weeks later, a Silverstone clamp was put on the right common carotid, but she immediately developed a severe left hemiparesis. The clamp was removed. She has done relatively well over the subsequent five years.

10. O.M. is a 57 year old man, who, eleven months prior to admission, suffered an attack of severe head pain. One month prior to admission, he had a sudden episode of blindness in the right eye lasting ten minutes. He was admitted because of an attack of head pain and lethargy, and a neurological examination revealed an organic mental syndrome, stiff neck, and a small but reactive left pupil. Spinal fluid revealed xanthochromic fluid. A right carotid angiogram revealed an aneurysm of the left anterior cerebral artery being fed by the opposite side. A left carotid angiogram revealed an aneurysm of the left anterior cerebral artery. One week later, surgery was performed with excision of the aneurysm. However, the following day, he did very poorly and had to be reoperated on, at which time bilateral epidural hematomas were found and it was necessary to do a left frontal lobectomy at this time. Following convalescence, three weeks later, repeated angiography was performed and both vascular trees were normal. However, his general neurological condition has been bad, especially with reference to his mental state, and he has been an in-patient of a state hospital since discharge.

11. J.M., a 57 year old man, developed a relatively sudden left hemiparesis six weeks prior to admission. At hospitalization, there was evidence of a left hemimotor syndrome. Cerebrospinal fluid was xanthochromic. A right carotid angiogram revealed an aneurysm of the middle cerebral artery. He had a craniotomy with excision of this lesion. Except for a mild convulsive disorder, he did well for six years and then died of a coronary occlusion.

12. L.K., a 52 year old woman, was admitted in coma of four hours' duration. At that time, she also had a left hemiparesis. Cerebrospinal fluid was bloody. She was treated conservatively and did well, until the twentieth hospital day, when she had a convulsion and again lapsed into coma. At that time, a lumbar puncture revealed bloody fluid. A right

carotid angiogram demonstrated an infraclinoid aneurysm of the internal carotid artery. The right common carotid artery was ligated. She did very poorly over the next four days and an intracranial space-occupying lesion was suspected. A craniotomy uncovered not only a subdural hematoma, but also an intracerebral hematoma. Five days later, there was another episode of intracranial bleeding. She finally stabilized, but was left with marked neurological deficits five years after discharge.

13. D.G., a 57 year old woman, suffered a severe attack of head pain one month prior to admission and, five days prior to hospitalization, she had recurrent head pain and ptosis of the right eyelid. On admission, she had a severe organic mental syndrome, a left hemimotor syndrome, and a right third nerve palsy. Cerebrospinal fluid was bloody. On the sixth hospital day, a right carotid angiogram revealed an aneurysm of the internal carotid artery at the junction of the posterior communicating artery. The following day, a Silverstone clamp was applied to the right common carotid artery. She had done well four years after discharge.

14. R.F., a 57 year old hypertensive woman, had a severe attack of head pain and confusion two weeks prior to admission. Lumbar puncture at that time revealed bloody fluid. On admission, she had a stiff neck, an organic mental syndrome, and bilateral papilledema. The spinal fluid was xanthochromic. One week later, a right carotid angiogram was suspicious of an aneurysm of the anterior communicating artery. Three days later, a left carotid angiogram revealed the aneurysm of the anterior communicating artery. A vertebral angiogram was normal. Three weeks later, a craniotomy was performed and the aneurysm was clipped. The lesion was also packed with muscle. One month thereafter, a repeat left carotid angiogram still demonstrated the aneurysm—the hypaque seemed to pass through the clip on the feeding vessel. She has done relatively well two years and four months following surgery.

15. Case R.M., a 75 year old woman, had developed severe head pain and a stiff neck six years before admission. Angiography at that time revealed an infraclinoid aneurysm of the left carotid artery. The left common carotid artery was clamped, but because of the immediate development of a hemiparesis, it was removed. Six years hence, there was recurrence of head pain and a stiff neck. On admission, she had a severe organic mental syndrome and a left sixth nerve palsy. A spinal tap revealed bloody fluid. Her course was progressively downhill and she died six days later.

One cannot judge surgical results from so few patients. However, these patients do depict the formidable problems which exist. Surgery attempted when patients are critically ill is usually done in desperation, and neurosurgeons, as well as neurologists, are aware of this. With the new techniques of hypothermia, hypotension and transient avascular surgery (15, 16), it is expected that neurosurgical patients will have less morbidity and mortality.

In the above series of operative cases, six patients had craniotomies and clips applied to the aneurysms. One patient had a hemorrhage from a blood vessel tear as the clip was applied. Three patients had postoperative angiography, which revealed that the clip was not effective. Two patients did well, but one patient did not have angiography after surgery and cannot be completely evaluated, especially in view of the other results.

Two patients were operated on in critical condition and current neurosurgical thinking tends to avoid surgery under such circumstances.

Two patients had successful excision of the aneurysms. However, in one patient, complications of the most severe nature occurred, namely, epidural hemorrhage, which required reoperation and a left frontal lobectomy. Consequently, the patient has become a permanent resident in a state mental institution.

Two patients, both of whom had ligations of the common carotid artery, unfortunately also developed subdural hematomas. Consequently, they had craniotomies and both were left with marked neurological deficits. Apparently, in these two cases, the subarachnoid hemorrhage caused the blood clots.

Five patients had Silverstone clamps applied to the common carotid artery. Two of these patients had immediate postoperative hemiparesis and the clamps had to be removed. Similar problems with this technique have been reported (17). One patient, R.M., died of a recurrent hemorrhage at the age of 75, six years after the initial bleeding episode. Of the three patients who have done well, one had the clamp removed four months after surgery. None of these patients have had recurrent hemorrhage. Incidentally, none of these patients had angiography done after the procedures.

The remaining two patients emphasize the need for complete angiography. One patient had an asymptomatic spontaneous occlusion of the other internal carotid artery. The other patient had an unsuccessful angiogram on the side of the aneurysm. When a pneumoencephalogram revealed a mass, a craniotomy was performed, because a neoplasm was suspected. Fortunately, a needle was inserted into the mass and, when blood was obtained, the operation was terminated.

Group II. Subarachnoid Hemorrhage due to Ruptured Intracranial Aneurysm

B. Conservatively treated patients

1. Twenty cases died during hospitalization (Table VI).

Of the twenty patients who died during hospitalization, ten of them were under fifty years of age. Six patients were admitted in critical condition and died shortly thereafter (1 day, 1 day, 2 days, 2 days, 3 days, 4 days). Two of the patients remained critically ill and apparently had recurrent hemorrhage before dying (5th and 7th hospital days; 6th and 9th days). The remaining two, ages twenty-nine and twenty-seven respectively, both had anterior cerebral artery aneurysms. The first had had a previous episode three years before this fatal one. He rebled on the ninth hospital day after doing well. The second patient had a recurrent hemorrhage on the seventeenth hospital day. Only these two patients actually present a controversy as to management, inasmuch as some neurosurgeons would most likely have preferred direct intervention.

Ten patients were over fifty years of age. Seven of them were critically ill on admission and died shortly thereafter (1 day, 1 day, 3 days, 7 days, 7 days, 7 days, 8 days). Interestingly, the postmortem examination of a hypertensive seventy year old man, who had subarachnoid hemorrhage, revealed actually no cause of bleeding. However, he is included in this series because he had an unruptured aneurysm of the middle cerebral artery. Of the remaining three patients, two suffered from hypertension. One of these patients, age sixty-five, had two additional bleeding episodes prior to dying on the twenty-first hospital day. The other patient, age sixty-two, succumbed on the thirtieth hospital day and two neurosurgeons, who had been called in in consultation, recommended

conservative management. The remaining patient, age sixty, remained critically ill until dying on the twenty-seventh hospital day. It seems that none of these patients would have been operated on according to present indications for operative intervention by most neurosurgeons.

2. Twenty-six cases—well following hospitalization (Table VII).

Twenty-six cases with proved aneurysms were treated conservatively. None of these patients have had recurrent hemorrhage since their last discharge from the hospital. However, the follow-up study is admittedly not long nor is it uniform in terms of duration for all patients. Six of these patients had had previous episodes of subarachnoid hemorrhage.

Of the thirteen patients under the age of fifty, four had aneurysms of the anterior communicating artery. This is considered a most difficult type of lesion to approach surgically, but new techniques are lowering the surgical mortality rate (18). Five other patients had multiple artery aneurysms. One of these patients, with bilateral supraclinoid internal carotid artery aneurysms, had a recurrent hemorrhage on the twelfth hospital day and has suffered from a severe organic mental syndrome. Three of the remaining four patients had aneurysms in the circulation of the dominant hemisphere (supraclinoid internal carotid artery aneurysm, posterior communicating artery aneurysm, infraclinoid internal carotid artery aneurysm). The latter patient, with the infraclinoid internal carotid artery aneurysm, was forty-four years of age and actually had bled eighteen years previously. She also had a recurrent hemorrhage on the twentieth hospital day, but is now well four years after hospitalization. The last patient had an aneurysm of the posterior communicating artery in the circulation of the left hemisphere. The three factors which mitigated against surgery in most of these patients were the multiplicity of the aneurysms, the location of an aneurysm on the anterior communicating artery, and the presence of aneurysms in the circulation of the dominant hemisphere.

Thirteen patients were over fifty years of age. Five of these patients suffered from hypertension and three of them had multiple aneurysms. There were an additional two patients, nonhypertensive, who also had multiple aneurysms. Of the remaining six patients, four had aneurysms in the circulation of the dominant hemisphere. The remaining two had an anterior communicating artery aneurysm and a supraclinoid aneurysm of the right internal carotid artery. Four of these thirteen patients had recurrent hemorrhages, which occurred three months, three years, eight years, and thirty years prior to the last episode. It is doubtful whether any of these thirteen patients would be considered today a candidate for surgical intervention.

Group III. Subarachnoid Hemorrhage of Unknown Cause

A. Surgically treated—four cases

Of those cases who had a subarachnoid hemorrhage and ruptured aneurysm could not be diagnosed, four patients were treated surgically. Their courses are as follows:

TABLE VI

Ruptured Intracranial Aneurysm—Conservatively Treated—Died

Case and Sex	Age	Admission Clinical Condition	Angiography			Course
			RC	LC	V	
S.W., F	47	II	ACe	ND	ND	Sudden head pain and stiff neck ten hours before admission. No neurologic findings. Bloody spinal fluid. Recurrent hemorrhage fifth hospital day and again seventh day, when she died. Postmortem denied.
J.V., M	29	III	ND	ND	ND	Similar episode occurred three years previously. Clinical state was stabilized until ninth hospital day, when he became suddenly comatose. Postmortem—ruptured multilobulated aneurysm of the left ACe at its junction with internal carotid artery.
S.G., F	27	III	NL	ND	ND	Patient stabilized over seventeen days, when she suddenly lapsed into coma and died. Postmortem—ruptured aneurysm of ACe at its junction with internal carotid artery.
J.R., F	49	IV	PCo	NL	ND	Recurrent hemorrhage sixth hospital day. Died on ninth day. Postmortem—ruptured aneurysm of PCo at the internal carotid artery.
E.C., F	47	III	ND	ND	ND	Critically ill until death on third hospital day. Postmortem—ruptured aneurysm ICsc. Similar unruptured aneurysm on right side.
W.T., M	38	IV	ND	NL	ND	Critically ill until death on fourth hospital day. Postmortem—aneurysm of ACo.
E.M., F	32	IV	ND	MCe	ND	Died within 24 hours of admission. Postmortem—ruptured aneurysm MCe.
L.O., M	44	IV	ND	ND	ND	Died within 24 hours of admission. Postmortem—ruptured aneurysm ACe. Also, unruptured aneurysm MCe.
A.R., M	33	IV	ND	ND	ND	Died within two days. Postmortem—ruptured aneurysm ACe. Also unruptured aneurysm MCe.
S.I., F	40	IV	ND	MCe	ND	Admitted in coma and died two days later. Postmortem—ruptured aneurysm MCe at circle of Willis. Unruptured aneurysm of right MCe.
J.M., M	65	IV	NL	ND	ND	Hypertensive. Recurrent hemorrhage on fourth hospital day and on ninth hospital day. Remained in a semi-comatose state until death 21 days after admission. Postmortem—ruptured aneurysm ACe at junction ACo.
R.A., F	60	III	ND	ICic	ND	Recurrent hemorrhage on fifth day. Stayed critically ill in semi-coma with convulsions until 27th hospital day, when she died. Postmortem—confirmed aneurysm ICic.

TABLE VI—*Continued*

Case and Sex	Age	Admission Clinical Condition	Angiography			Course
			RC	LC	V	
M.K., M	62	III	NL	MCe	ND	Hypertensive. Bilateral papilledema. Recurrent hemorrhage on fourth hospital day. Stabilized. Two neurosurgical opinions against surgery. Died following third hemorrhage on thirtieth hospital day. Postmortem—ruptured aneurysm MCe at circle of Willis.
M.V., M	50	IV	ND	ND	ND	Admitted in coma and died unchanged on seventh hospital day. Postmortem—aneurysm ACo.
F.L., M	65	IV	ND	NL	ND	Admitted in coma and critically ill until death on seventh hospital day. Postmortem—right MCe aneurysm at circle of Willis.
E.C., F	51	IV	ICse	ND	ND	Hypertensive. Severe organic mental syndrome and left hemiplegia on admission, which remained unchanged until death on seventh hospital day. Postmortem—ICse aneurysm.
M.R., F	50	IV	ND	ND	ND	Admitted in coma and remained critically ill until death on eighth hospital day. Postmortem—ACo aneurysm.
A.S., M	59	IV	ND	ND	ND	Four years previously suffered subarachnoid hemorrhage and right-sided neurologic findings. Admitted in coma and died three days later. Postmortem—ruptured left MCe aneurysm at circle of Willis.
M.M., F	58	IV	ND	ND	ND	Hypertensive. Admitted in coma and died within 24 hours. Postmortem—ruptured basilar artery aneurysm at the level of the inferior-posterior cerebellar artery.
A.N., M	70	IV	ND	ND	ND	Hypertensive. Admitted in coma and died in 24 hours. Postmortem—no cause of bleeding. Unruptured aneurysm of right MCe.

Code: Clinical condition Stage I. —Neurological signs without intracranial hemorrhage.
Clinical condition Stage II. —Intracranial hemorrhage without neurological signs.
Clinical condition Stage III.—Intracranial hemorrhage, neurological findings, but no marked disturbance of consciousness or sensorium.
Clinical condition Stage IV.—Intracranial hemorrhage with diminished level of consciousness and/or an organic mental syndrome.
RC—right carotid angiogram.
LC—left carotid angiogram.
V—vertebral angiogram.
ND—not done.
NL—normal.
ICic—infraclinoid internal carotid artery aneurysm.
ICsc—supraclinoid internal carotid artery aneurysm.
ACo—anterior communicating artery aneurysm.
ACe—anterior cerebral artery aneurysm.
MCe—middle cerebral artery aneurysm.
PCo—posterior communicating artery aneurysm.
PCe—posterior cerebral artery aneurysm.
B—basilar artery aneurysm.

Case A.F., a 47 year old woman, suddenly became stuporous a week before admission. A lumbar puncture at another institution revealed bloody fluid. Her condition progressively worsened and, when admitted, she was comatose. Cerebrospinal fluid at this time was xanthochromic. In a desperate hope of removing a possible intracerebral clot, a craniotomy was immediately performed. No such pathology was found and she died the following day. Postmortem permission was denied.

Case B.L., a 24 year old woman, had two attacks of severe head pain four and five weeks before hospitalization. The day prior to admission, double vision occurred. On admission, she had a right third nerve palsy and a stiff neck. The cerebrospinal fluid was bloody. A right carotid angiogram was unsuccessful. She improved, but two weeks later, she suddenly had a convulsion and rapidly became comatose. A lumbar puncture revealed bloody fluid. A right common carotid ligation was performed, but the patient expired that day. Postmortem permission was denied.

TABLE VII

Ruptured Intracranial Aneurysm—Conservatively Treated—Alive

Case and Sex	Age	Admission Clinical Condition	Angiography			Course
			RC	LC	V	
A.U., F	31	I	ICic	ICic	B	Hypertensive. Subarachnoid hemorrhage seven weeks before admission. On admission, she only had a left temporal field defect. Well 35 months after hospitalization.
M.G., F	43	I	NL	ICsc	ND	Subarachnoid hemorrhage eleven months previously. Seizure disorder. Well 38 months after hospitalization.
S.F., F	47	I	ACo	ACo	ND	Subarachnoid hemorrhage two months prior to admission. Right hemiparesis. Well 37 months after hospitalization.
H.H., F	48	II	ND	ACo	ND	Subarachnoid hemorrhage one month previously. Well forty months after hospitalization.
P.T., F	38	III	ICsc	ICsc	ND	Recurrent hemorrhage on twelfth hospital day. Discharged with severe organic mental syndrome. Condition unchanged 24 months after hospitalization.
D.G., M	36	I	ICsc	ICsc	ND	Subarachnoid hemorrhage one month previously. Patient was well for four years and died of carcinoma of the colon.
M.C., F	28	II	NL	PCo	ND	Patient well 19 months after hospitalization.
B.S., F	22	II	ICsc	NL	ND	Patient well 51 months after hospitalization.
S.S., F	39	III	ND	ICsc	ND	Patient well 42 months after hospitalization.
R.L., F	44	IV	NL	ICic	ND	First episode eighteen years previously. Recurrent hemorrhage on twentieth hospital day. Well 96 months after hospitalization.
A.B., M	41	IV	ACo	ND	ND	Patient well 77 months after hospitalization.
F.J., F	47	IV	ACo	ACo	NL	Patient well forty months after hospitalization.

TABLE VII—*Continued*

Case and Sex	Age	Admission Clinical Condition	Angiography			Course
			RC	LC	V	
S.D., F	48	IV	MCe	NL	ND	Patient had two aneurysms on the right middle cerebral artery. Well 14 months after hospitalization.
I.B., M	66	IV	ND	ICie	ND	First subarachnoid hemorrhage eight years previously. Patient has done well seven months after hospitalization.
R.B., F	50	III	ICie	ICie	ND	Hypertensive. Subarachnoid hemorrhage three years previously. Patient well 34 months after hospitalization.
M.M., F	52	IV	NL	ICie	ND	Patient well 22 months after discharge, except for hemiparesis.
A.M., F	51	IV	ICse	NL	ND	Patient well forty months after hospitalization.
F.B., M	51	IV	ACo	ACe	NL	Hypertensive. Subarachnoid hemorrhage thirty years previously. Discharged with a severe organic mental syndrome and left hemiparesis, which is the same 28 months after hospitalization.
B.C., F	60	IV	ICse	ND	ND	Hypertensive. Well 46 months after hospitalization.
S.B., M	58	IV	NL	MCe	NL	Patient well 48 months after hospitalization.
C.M., F	65	IV	ACe	ND	ND	Hypertensive. Recurrent hemorrhage three months after discharge, but did well. He has stabilized 36 months since last hospitalization.
C.S., M	67	IV	ND	ICie ACe MCe	ND	Hypertensive. Patient had three aneurysms in the distribution of the left internal carotid artery. Discharged with aphasia and right hemiparesis. Well twelve months after hospitalization.
C.C., F	59	IV	ICse	ICse	ND	Patient well 33 months after hospitalization.
S.K., M	53	III	ACo	ACo	ND	Patient well 72 months after hospitalization.
T.L., M	56	IV	ACo MCe MCe	ND	ND	In spite of three aneurysms, in the right internal carotid circulation, he has done well 29 months since hospitalization.
S.G., F	54	IV	ND	ICse	ND	Patient well 36 months since hospitalization.

Case M.G., a 53 year old man, had a severe attack of head pain with unconsciousness one month prior to admission. Upon hospitalization at another institution, a lumbar puncture revealed bloody fluid. Right and left carotid angiograms were performed and they both were normal. Upon admission to this institution, there were no neurological findings. A Silverstone clamp was placed on the right common carotid artery and he has done well six years subsequently.

Case B.R., a 25 year old woman, had an episode of severe head pain five years ago. A

lumbar puncture was reported to reveal bloody fluid. (Clinical information was not available.) A right carotid angiogram was done and the right common carotid artery was ligated. She is listed in this series because she came to the attention of the Neurological Service when she was admitted to this hospital because of a convulsive disorder, as well as a severe paranoid state. Because of the latter conditions, a neurologic diagnostic investigation could not be performed.

Group III. Subarachnoid Hemorrhage of Unknown Cause

B. Conservatively treated

1. Fourteen cases—died during hospitalization (Table VIII).
2. Thirty-five cases—well following hospitalization (Table IX).

The major difficulty in evaluating these patients is the lack of complete information. Most patients did not have total angiography. Only four of sixteen patients who died were autopsied. It seems likely that some of these patients suffered from hemorrhage due to aneurysm, but the pathology was not demonstrated.

Of the sixteen patients who died of subarachnoid hemorrhage of unknown cause, fifteen were admitted in critical condition. They died shortly thereafter. The severity of each illness and the rapidity of fatal outcome limited angiography to three patients. Surgical procedures in two cases were desperate measures. Actually, in one of them, case B.L. age twenty-four, a right carotid angiogram was unsuccessful. Perhaps if it had been repeated while she was well and prior to her last hemorrhage, an aneurysm may have been discovered. The sixteenth patient, case M.R., age 48, refused all studies and would not consider surgical intervention, even if pathology had been found.

Postmortem examinations were performed in five cases. No source of bleeding was found in three patients. One was a 58 year old hypertensive man. In the two other patients, aneurysms were strongly suspected, but were not found. One was age 34 and had a massive subarachnoid hemorrhage; he died within 24 hours of admission. The other, age 45, had two recurrent hemorrhagic episodes during nine days of hospitalization prior to death. Case M.M. suffered from a sudden subarachnoid hemorrhage, but postmortem examination revealed an arterial carotid artery thrombosis and a transverse sinus thrombosis. The autopsy on the patient with a severe malabsorption syndrome revealed no source of bleeding, but multiple areas of encephalomalacia, with concomitant thrombosis of many small blood vessels.

Thirty-seven patients with undiagnosed cause of bleeding have done well.

The two patients who underwent surgery were unusual because complete information was lacking. A 53 year old man had his right common carotid artery clamped after a neurological investigation, including normal bilateral carotid arteriograms. It was thought the right internal carotid artery at its bifurcation was suspicious for an aneurysm. The reason for the decision to operate was not clearly defined in the case record. Case B.R., a 25 year old woman, gave the history of subarachnoid hemorrhage and a carotid artery ligation five years previously at another hospital. She was a paranoid schizophrenic individual

TABLE VIII

Spontaneous Subarachnoid Hemorrhage—Unknown Cause—Conservatively Treated—Died

Case and Sex	Age	Admission Clinical Condition	Angiography			Course
			RC	LC	V	
M.R., F	48	I	ND	ND	ND	Severe head pain two weeks prior to admission. Spinal fluid was xanthochromic. No neurological findings on admission. Permission for studies not granted. Patient died suddenly, in coma, 42 days after hospitalization, following a sudden severe headache. No postmortem.
E.M., F	44	IV	NL	ND	ND	Admitted in stupor and died on first hospital day.
M.M., F	46	IV	NL	NL	ND	Patient remained critically ill and her course was progressively deteriorating. Postmortem revealed thrombosis of the right middle cerebral artery and thrombosis of the left lateral transverse sinus.
L.S., F	45	IV	NL	ND	ND	Patient's critical state worsened due to recurrent bleeding on the fourth and eighth hospital days. Died on ninth day. Postmortem revealed no source of bleeding.
L.R., F	46	IV	ND	ND	ND	Hypertensive. She remained critically ill and progressively deteriorated, dying on the ninth hospital day. Postmortem refused.
G.K., F	40	III	ND	ND	ND	Hypertensive. Patient only had a right third nerve palsy. Suddenly died on fifth hospital day. Postmortem refused.
M.R., M	48	IV	ND	ND	ND	Patient admitted in coma and died within twenty-four hours. Postmortem refused.
G.R., M	34	IV	ND	ND	ND	Patient admitted in coma and died within twelve hours. Postmortem—no source of hemorrhage.
L.S., M	58	IV	ND	ND	ND	Hypertensive. Patient admitted in coma and died within twenty-four hours. Postmortem—no source of hemorrhage.
M.D., F	56	IV	ND	ND	ND	Hypertensive. Admitted in coma and died within twenty-four hours. Postmortem denied.
M.B., F	62	IV	ND	ND	ND	Hypertensive. Patient had severe confusion, a right third nerve palsy, a left hemiparesis. Died within twenty-four hours. Postmortem denied.
F.K., F	62	IV	ND	ND	ND	Hypertensive, admitted in coma and died twenty-four hours later. Postmortem denied.
R.B., F	63	IV	ND	ND	ND	Hypertensive, admitted in coma and died within twenty-four hours. Postmortem denied.
I.D., M	53	IV	ND	ND	ND	Patient had a background of severe malabsorption syndrome and suddenly went into coma and died within twenty-four hours. Postmortem revealed diffuse encephalomalacia.

and her records were not obtainable, so nothing could be stated as to what led to the surgical intervention.

The 35 conservatively treated patients, who are still alive, exhibit one feature which is somewhat distinct from those conservatively treated, undiagnosed pa-

TABLE IX

Subarachnoid Hemorrhage—Unknown Cause—Conservatively Treated—Alive

Case and Sex	Age	Admission Clinical Condition	Angiography			Course
			RC	LC	V	
J.A., M	44	I	NL	NL	NL	Subarachnoid hemorrhage two months previously. On admission, he only had an organic mental syndrome. Well 24 months after hospitalization.
B.R., F	27	III	NL	ND	ND	Two week history of sudden onset of blurred vision. Patient had papilledema and right sixth nerve weakness. Well 44 months after hospitalization.
J.W., M	48	IV	NL	ND	ND	Sudden onset of convulsions and development of a left hemiparesis. Patient well ninety months after hospitalization.
S.A., M	41	IV	ND	ND	ND	Sudden onset of head pain. Patient had a left third nerve palsy and a right hemiparesis, with nystagmus, left palatoplegia. Well 38 months after hospitalization.
A.A., M	38	III	NL	NL	ND	Hypertensive, right hemi-motorsensory syndrome. Patient well 42 months after hostalization.
S.K., F	26	IV	NL	ND	ND	Sudden onset of head pain and aphasia. Well sixty months after hospitalization.
S.S., M	47	II	NL	ND	ND	Subarachnoid hemorrhage without neurological findings. Patient well 31 months after hospitalization.
J.L., M	48	II	*	NL	ND	Hypertensive, sudden onset of low back pain six days before admission. He then developed a headache and a stiff neck. Clinical course one of a myelopathy. Patient unchanged 35 months after hospitalization.
M.R., F	21	IV	ND	ND	ND	Sudden onset of head pain and an organic mental syndrome. Patient refused procedures. Well thirty months after hospitalization.
D.A., F	28	IV	NL	ND	ND	Sudden head pain with lethargy. Patient had a left homonymous field defect. Discharged, but had a recurrence one year later with right eye pain. Well fifteen months after last hospitalization.
M.M., F	48	IV	NL	*	ND	Sudden head pain with confusion. Well eighty months after hospitalization.
R.G., F	48	IV	ND	ND	ND	Severe hypertensive, 280/160, admitted with convulsions followed by severe confusion and right hemiparesis. Recovered, but died suddenly at home five months later, after suddenly going into coma.
S.A., M	40	IV	*	NL	ND	Hypertensive, sudden onset of unconsciousness followed by severe confusion. Well thirty months after hospitalization.
R.J., M	43	IV	NL	NL	NL	Two previous episodes of subarachnoid hemorrhage. On last admission, sudden head pain with organic mental syndrome. Well 35 months after hospitalization.
J.H., M	44	IV	NL	NL	ND	Hypertensive. Sudden onset of confusion with a left hemiparesis. Bloody spinal fluid. Well 42 months following hospitalization.
C.U., M	53	I	ND	ND	ND	History of noises and decreased hearing for ten years. Neurological examination revealed left fifth, seventh and eighth nerve impairment. On fifth hospital day, 24 hours after a pneumoencephalogram, he had a sudden onset of head pain and a stiff neck. Uneventful recovery. Well eighteen months after hospitalization.

TABLE IX—*Continued*

Case and Sex	Age	Admission Clinical Condition	Angiography			Course
			RC	LC	V	
H.D., F	52	I	NL	NL	NL	Hypertensive, subarachnoid hemorrhage two months prior to admission. On admission, she only had a left third nerve weakness and clumsiness of the left hand. Well twenty months after hospitalization.
V.B., F	63	III	ND	ND	ND	Sudden onset of head pain. Bilateral Babinski signs. Procedures refused. Well 93 months after hospitalization.
A.K., M	50	III	NL	NL	ND	Sudden onset of head pain and weakness of left upper extremity. Well 84 months after hospitalization.
E.G., M	63	III	ND	ND	ND	Sudden onset of pain over right eye and poor vision. Left homonymous field defect. Procedures refused. Patient well 48 months after hospitalization.
S.B., M	58	III	NL	ND	ND	Hypertensive, 240/140, left facial weakness. Patient well fifty months after hospitalization.
J.V., F	64	II	ND	ND	ND	Sudden onset of head pain three days before admission. Proeedures refused. Patient well 49 months after hospitalization.
J.A., F	66	I	NL	ND	ND	Sudden onset of pain in the buttoeks. Positive Kernig sign. Patient well 45 months after hospitalization.
F.C., M	56	I	NL	NL	ND	Sudden onset of head pain, positive Kernig sign. Patient well 23 months after hospitalization.
S.H., F	50	I	NL	NL	NL	Sudden onset of head pain. Three days later, sudden onset of aphasia and right hemiparesis. Patient gradually improved and well 22 months after hospitalization.
E.G., F	59	IV	NE	ND	ND	Hypertensive. Sudden onset of eonfusion and lethargy, with left hemiparesis. Permission refused for procedures. Patient well 36 months after hospitalization.
R.N., F	52	IV	*	ND	ND	Sudden onset of head pain and eonfusion. Patient well 87 months after hospitalization.
G.S., M	70	I	ND	ND	ND	Sudden onset of head pain and stiff neek. Proeedures refused. Patient well seventy months after hospitalization.
I.T., F	62	III	ND	NL	ND	Sudden onset of head pain and aphasia. Patient also had a right hemisensory syndrome. Patient stabilized one month after diseharge.
D.S., M	54	IV	NL	NL	NL	Hypertensive. Sudden onset of head pain and aphasia. Patient also had a left hemisensory syndrome. Patient well eighteen months after hospitalization.
M.P., F	60	III	ND	ND	ND	Sudden onset of head pain followed by eonfusion. Dilated right pupil. Proeedures refused. Patient well 29 months after hospitalization.
M.Y., F	57	IV	ND	NL	ND	Hypertensive, 210/140. Sudden onset of eonfusion and drowsiness, with right hemiparesis. Patient well 32 months after hospitalization.
H.M., F	50	IV	NL	ND	ND	Sudden onset of head pain and organic mental syndrome. Admitted in semi eoma. Bilateral Babinski signs. Patient well fifty months after hospitalization.
A.Z., M	50	IV	ND	ND	ND	Sudden onset of eoma. Patient also had a left third nerve lesion. Upon recovering eonseiousness, patient was also noted to have aphasia and a right hemiparesis. Did well for sixty months. Died of eardiopulmonary disease.
C.A., F	52	III	ND	ND	ND	Sudden onset of eonfusion and stiff neek. Patient well one month after hospitalization.

* Unsuecessful.

tients who died, *i.e.*, all but three patients were not as ill initially at the time of hospitalization.

There were no significant differences in the various patterns of neurological findings to distinguish these patients from those who suffered from aneurysms. Nevertheless, most likely some of them had such pathology.

It is to be noted that one patient, case R.G., age 48, died five months after hospitalization. Angiography was not done because she had malignant hypertension, with her blood pressure readings averaging approximately 280/160. Apparently, she succumbed to another intracranial hemorrhage while at home.

Case J.L., age 48, was unusual. He seemed to have a subarachnoid hemorrhage from a spinal cord lesion. He initially developed low back pain. A lumbar puncture revealed bloody fluid. A few days later, he became confused. This cleared, but a progressive myelopathy developed. A subsequent laminectomy revealed adhesive arachnoiditis, but no source of bleeding.

SUMMARY

The detailing of the course of these 125 patients cannot result in any definite conclusions as to the management of the clinical entities. The number of patients is too small. There are many gaps of knowledge due to the lack of total angiography and incomplete autopsy data. Nevertheless, certain features are noteworthy.

In the limited surgical experience, the incidence of complication was high—including inadvertent tearing of a blood vessel while clipping an aneurysm and neurological sequelae following the application of a Silverstone clamp. Placement of a clip on the neck of an aneurysm does not always succeed in blocking the blood supply to the lesion (three failures in six cases).

Two patients died following surgery, but they were critically ill prior to the operation. Today, the neurosurgical opinion tends to wait until active bleeding ceases.

Only two of the twenty patients with proved aneurysms, who were treated conservatively, may have been managed differently. The others, due to varying combinations of factors, such as the acuteness of the subarachnoid hemorrhage, their critical clinical condition, their age, and the presence of hypertension, would not be considered candidates for surgical intervention.

Most important, there are 26 patients with aneurysms who have done well without surgery. Another follow-up study is planned, but it seems that patients can live far longer than has been previously suspected after symptoms indicating a ruptured aneurysm have ensued. In this small series, one patient, age 51, has been well thirty years after a subarachnoid hemorrhage due to ruptured aneurysm, and another patient, case R.L., age 44, has been well eighteen years after an initial bleeding episode.

It is interesting that the hypertensive patients in this group had a high incidence of aneurysms—18 of 35 individuals. Apparently, high blood pressure is a contributing factor to the rupture of an aneurysmal sac. Consequently, the hypertensive patient who bleeds intracranially should be considered as possibly having an aneurysm.

In Group II, subarachnoid hemorrhage due to aneurysm, and Group III, subarachnoid hemorrhage of unknown cause, there was some parallel with respect to the severity of the illness and prognosis. In each group, a preponderant number of those conservatively treated who died were critically ill from the onset of illness to death. Almost none of them would be considered good operation risks.

Patients who have experienced a subarachnoid hemorrhage due to ruptured aneurysm and survived the acute illness have a varying prognosis when treated conservatively. No conclusion can be drawn, but it seems that their future is not as dim as has been depicted in the past.

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Gross Distribution of Atheroma in Clinical Peripheral Vascular Disease

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During the two year period of 1959–1960, 320 patients seen at the Peripheral Vascular Disease Clinic at St. Mary's Hospital, London, required investigation of moderate or severe lower limb ischemia due to atherosclerosis. Physical examination and arteriography were carried out on all these patients, and the resultant findings are reported herewith.

TABLE I

Analysis of distribution of atheroma in the lower extremities of 320 patients with 364 affected lower limbs

Diagnosis (Most Severely Diseased Vessel)	Number of Pts.		Total No. of Pts.	Percentage of all Pts., %	Total No. Affected Legs	Percentage of Affected Legs, %
	Unilateral Disease	Bilateral Disease				
Lower abdominal aorta	22	—	22	6.8	—	—
Iliac artery	44	7	51	15.9	58	15.9
Ilio-femoral arteries	6	—	6	1.9	6	1.7
Femoral artery	124	55	179	56	234	64.3
Femoro-popliteal arteries	16	3	19	6.0	22	6.0
Popliteal artery	29	1	30	9.4	31	8.5
Calf arteries	9	—	9	2.8	9	2.5
Foot/toe arteries	4	—	4	1.2	4	1.1
Total	254	66	320	100	364	100

Clinically, three main patterns of atherosclerosis were recognized. Aorto-iliac disease commonly presented with calf, thigh and/or buttock claudication, absent femoral pulses, and almost invariably complete absence of arterial pulses below this level. Femoropopliteal disease usually presented with calf claudication, although ischemic pain might be most marked in the foot, or present at both sites. It was not possible to distinguish clinically between superficial femoral and popliteal artery occlusion, although the latter was more likely to produce severe distal ischemia. In both groups, a good femoral pulse was present, no other leg pulses were palpable, and there was frequently additional disease of the calf vessels. Occlusion of the small vessels of the foot or toes was generally present with severe, but well-localized symptoms and signs. One or several painful and numb toes, with discoloration, coldness and tissue loss in the presence of ankle pulses, describes the picture most commonly

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FIG. 1. Typical block of superficial femoral artery at the adductor hiatus.

seen. The presence of an audible systolic bruit over a major artery was taken as confirmatory evidence of arterial narrowing.

METHODS AND RESULTS

A diagnosis was made for each patient from the history and physical examination. Lumbar aortography, or femoral arteriography was performed, and

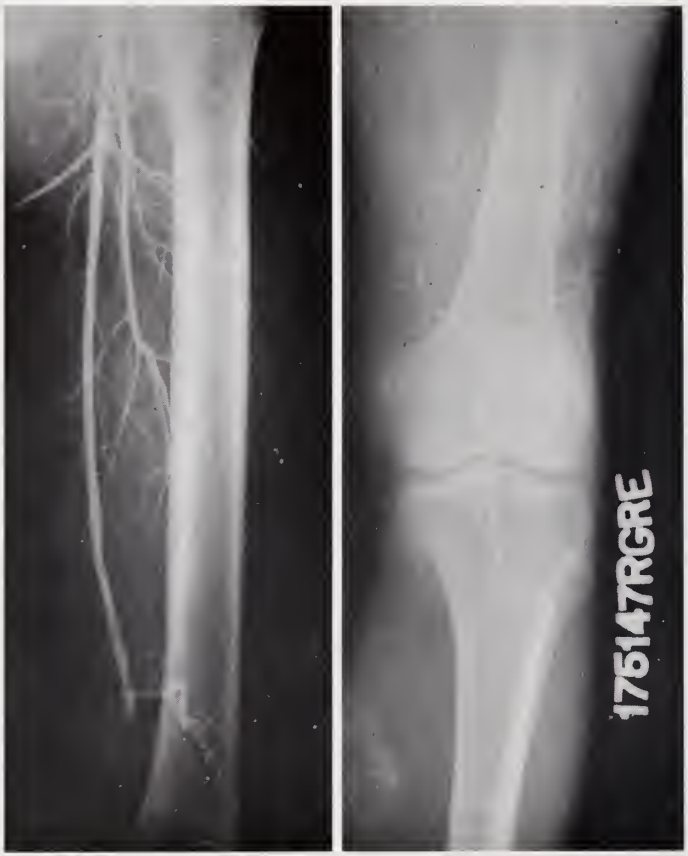

FIG. 2. Occlusion of lower segment of superficial femoral artery and upper third of popliteal artery.

the final diagnosis was then formulated on the basis of the most severely affected segment of artery. The results of these investigations are shown in Table I.

DISCUSSION

The commonest manifestation of atherosclerosis in the vessels to the lower limb is partial or complete occlusion of the superficial femoral artery (64.3%). Similar figures are presented by Lindbom (1) who found femoral artery disease to be the principal location in an examination of 356 femoral arteriograms, and by Mavor (2), who found the site of arterial occlusion in 150 leg claudicators to

be in the superficial femoral artery in 85 per cent of his patients (Figs. 1, 2). Haimovici, Schapira and Jacobson reported a series of 102 consecutive femoral arteriograms with 36.4 per cent femoral artery occlusions and 32.7 per cent popliteal artery occlusions, but lesser degrees of atherosclerosis are not discussed (3). Bloor, in reviewing approximately 1,500 patients, found femoral occlusions in 36.1 per cent, but adds that severe generalized arterial narrowing was present in an additional 25.1 per cent of patients (4).

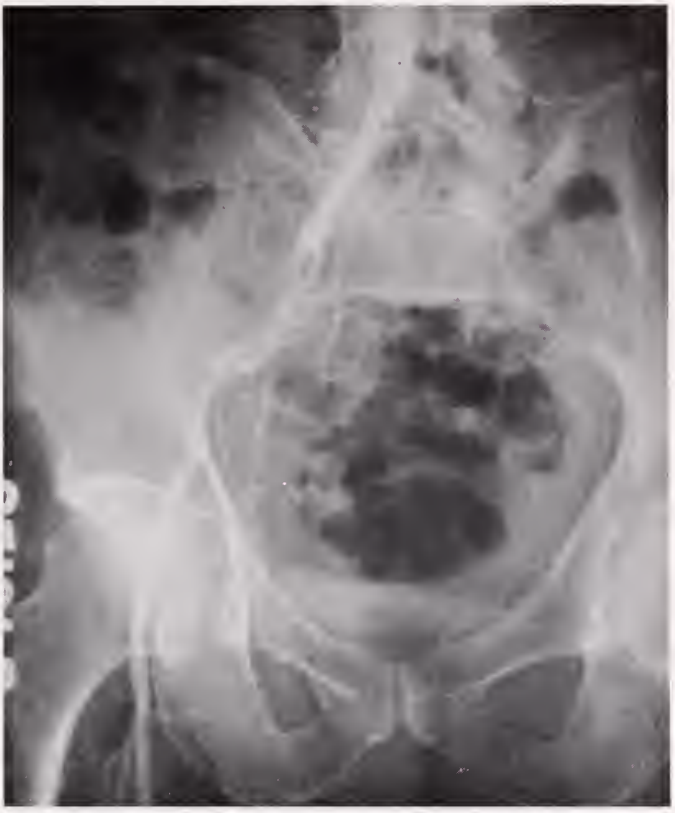

FIG. 3. Atheromatous irregularity of aortic bifurcation and complete occlusion of the left common iliac artery.

Disease in the lower abdominal aorta and iliac arteries is frequently found together, although narrowing or occlusion is often confined mainly to one or the other area (Fig. 3). Clinically and radiographically this region is best considered as one group. According to the present investigation, the next most common localization of atheroma is, therefore, in the aorto-iliac region (22.7%). These figures are similar to those of another large follow-up study, by Singer and Rob, where the incidence of atherosclerosis in this region was 30 per cent of 359 patients (5). Other comparable unselected series of patients with aorto-iliac or femoropopliteal disease are few, although Bloor finds a much lower incidence (5.8%) of combined aorto-iliac atheroma in his group (4).

Popliteal artery disease (8.5%, Fig. 4) and distal vessel disease (3.6%) were not common in this group of patients. This may be related to the low incidence of diabetes mellitus in this series (5.3%). Bilateral symptomatic atherosclerosis was found in 31 per cent of patients with femoral artery occlusions, and in 13.6 per cent of patients with iliac artery disease. The true incidence of bilateral lower limb atheroma is probably higher, but was only proved in patients whose

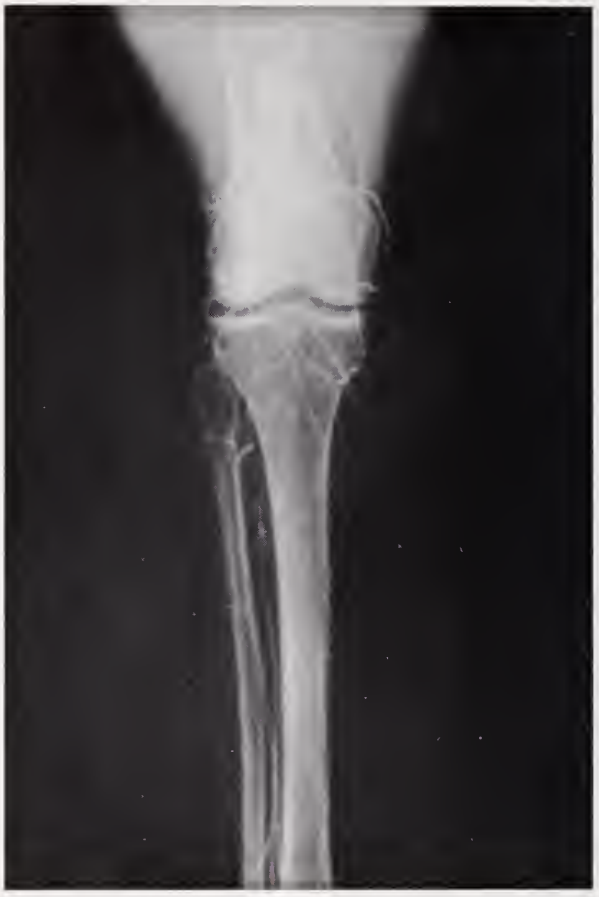

Fig. 4. Occlusion of lower half of popliteal artery with numerous collateral vessels.

symptoms and physical signs in the less severely affected leg warranted arteriography.

CONCLUSIONS

These findings stress the importance of an accurate anatomical diagnosis in patients with severe lower limb ischemia. When the major obstruction lies below the popliteal artery, direct arterial surgery has little to offer with current methods (6).

Above this level, femoral, and some cases of popliteal artery occlusion often

can be relieved by by-pass grafting or thromboendarterectomy (7). Even greater success can be expected when these methods are applied to lesions in the aorto-iliac region (8).

SUMMARY

A personal experience of 320 patients with peripheral atherosclerosis is presented. All patients were investigated by clinical examination and arteriography. The incidence and gross distribution of atheromatous lesions in the arteries to the lower limbs are analysed. The commonest site of arterial disease was found to be the superficial femoral artery.

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Unusual Sites for "Segmental" Cerebrovascular Occlusion

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In recent years, much has been written about the "segmental" nature of occlusive cerebrovascular disease and its predilection for the origin of great

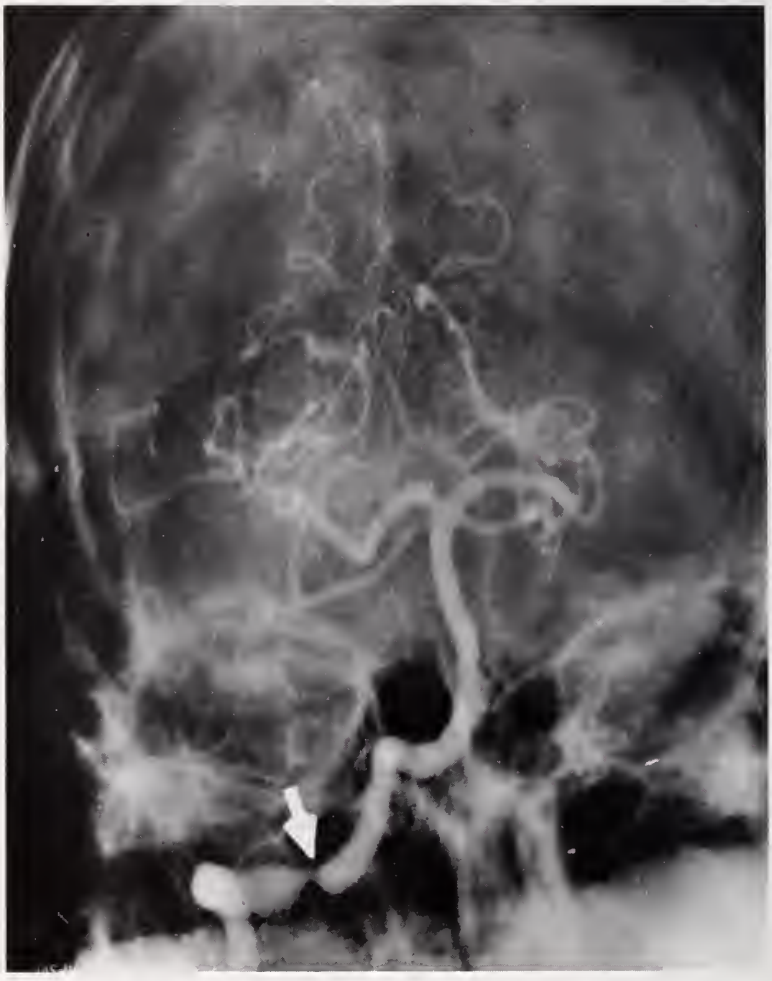

FIG. 1. Right vertebral arteriogram showing a segmental occlusion (arrow) of the right vertebral artery at the atlas.

vessels (1, 2). Several arteriographic (3, 4) and postmortem (5, 6) studies have indeed shown that when a local area of arteriosclerotic stenosis is present, it

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is generally located close to the origin of a large artery, especially the internal carotid or vertebral artery.

The purpose of this communication is to draw attention to the occurrence of "segmental" occlusions at other sites. Three patients with unusual arteriographic findings are reported.

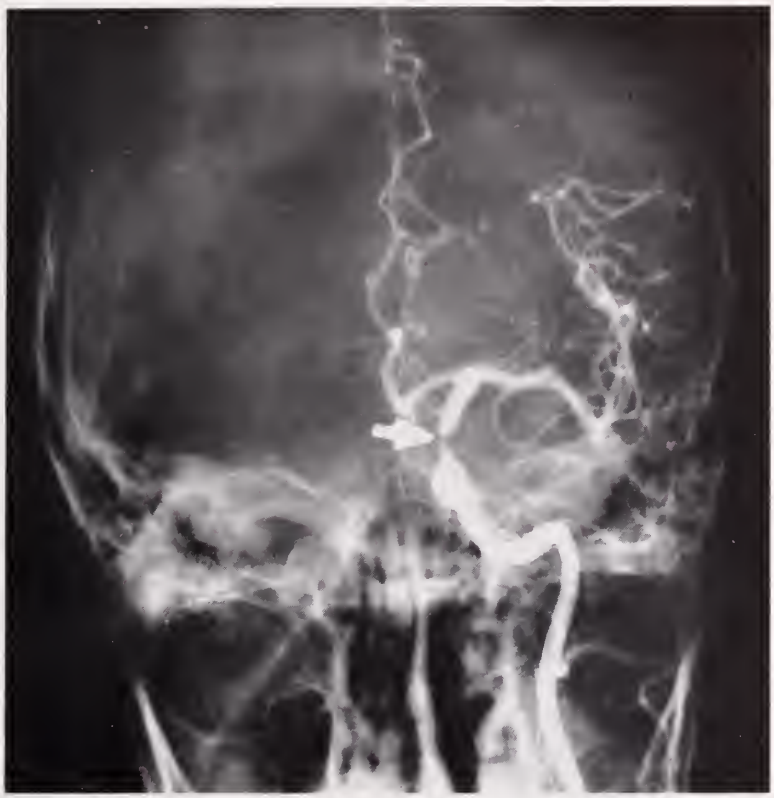

FIG. 2. Left common carotid arteriogram showing a segmental occlusion (arrow) of the supraclinoid portion of the internal carotid artery.

CASE 1

A 48 year old man was admitted for episodes of jagged, shimmering "flashes" in his left field of vision for one month. Three weeks prior to admission, he had noticed a persistent impairment of vision in the left field, and had complained of numbness of the left foot and left hand for two weeks. There was a background of hypertension and angina.

The neurologic examination indicated a left homonymous hemiamblyopia for color and the plotted central fields of vision revealed left homonymous scotomata. The cerebrospinal fluid protein was 83 mg%. Other preliminary laboratory data, including an electroencephalogram, were normal. A percutaneous right vertebral arteriogram disclosed a localized area of narrowing in

the right vertebral artery at the level of the atlas (Fig. 1). The remainder of the circulation was normal. Permission for further study was refused.

CASE 2

A 61 year old man had several transient attacks of right hemiparesis for two months prior to admission. Episodes of aphasia began two weeks prior to hos-

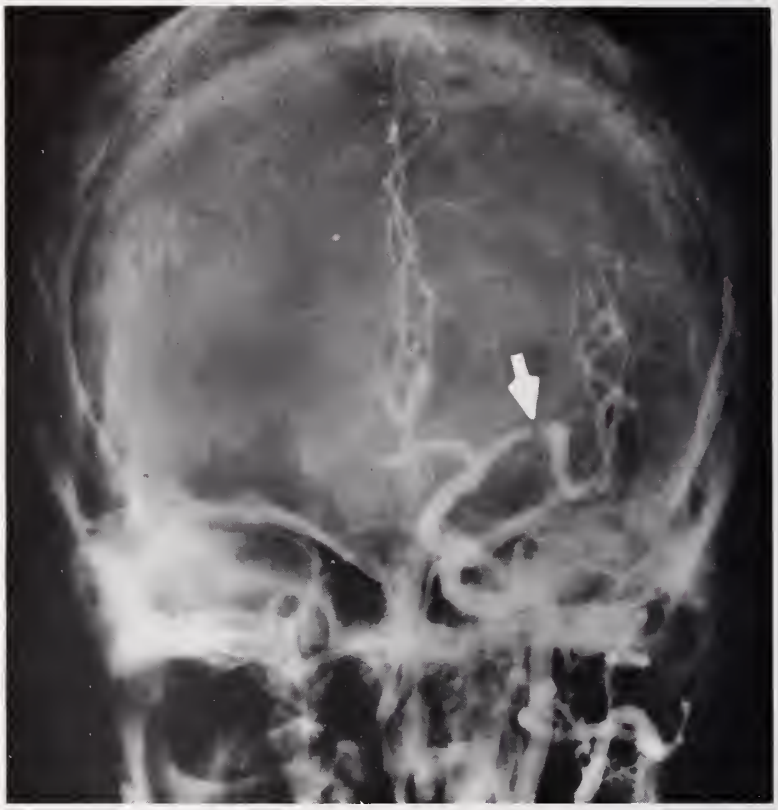

FIG. 3. Left common carotid arteriogram showing a segmental occlusion (arrow) of the first portion of the middle cerebral artery.

pitalization and finally led to admission. There was a past history of hypertension.

The neurologic examination, including measurement of retinal artery pressures, was normal. An electroencephalogram showed a focal left temporal abnormality. Other preliminary laboratory data were normal. A left carotid arteriogram revealed focal stenosis of the supraclinoid portion of the internal carotid artery (Fig. 2). No abnormalities were noted elsewhere in the arterial tree.

CASE 3

A 63 year old man was hospitalized because of right hemiparesis and aphasia of one week's duration. Generalized convulsions had begun seven years prior to admission. There had been progressive mental changes for two years. The

FIG. 4. Common carotid arteriogram showing an aneurysm of the anterior cerebral artery and areas of narrowing at the supraclinoid portion of the internal carotid artery and first portion of the middle cerebral artery. The patient was investigated for a recent subarachnoid hemorrhage. The areas of narrowing are presumed to be due to spasm, and not due to "segmental" occlusions.

right hemiparesis, while of sudden onset, had progressed during the week prior to admission. The patient was diabetic and had previously undergone surgery for repair of a detached retina.

Neurologic examination revealed aphasia, right hemiparesis, right hemisensory syndrome and right extensor plantar response. The fasting blood sugar was 174 mg% and the spinal fluid protein 82 mg%. Roentgenograms of the

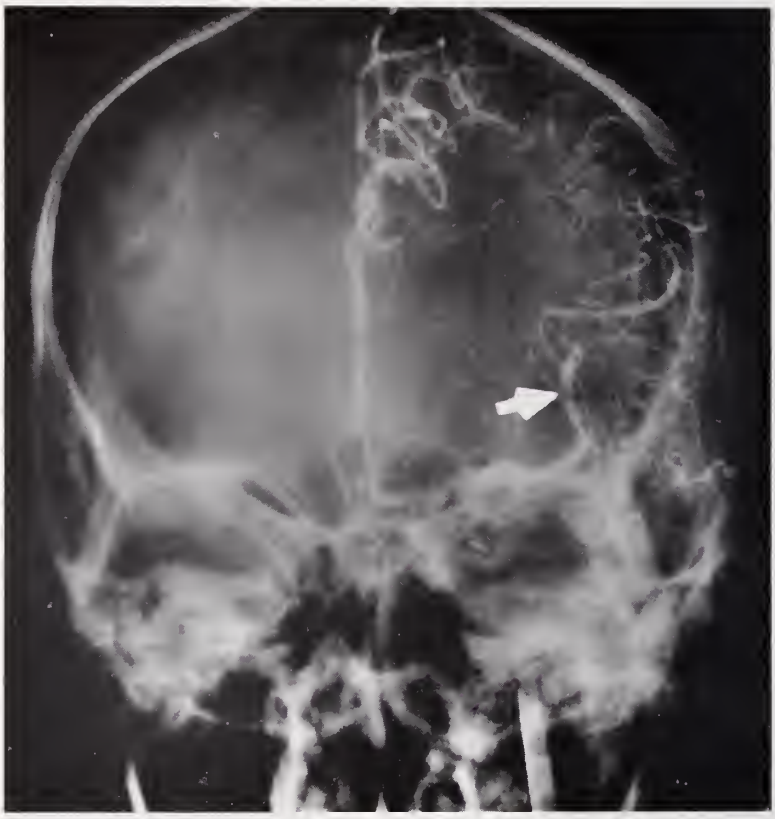

FIG. 5. Common carotid arteriogram showing a localized area of narrowing (arrow) in the main trunk of the middle cerebral artery. This patient experienced a recent subarachnoid and intracerebral hemorrhage. At autopsy, the caliber of the middle cerebral artery was normal throughout. This is felt to be a case of proved "spasm."

skull showed metallic densities in the left orbit presumably related to the previous retinal surgery. A left carotid arteriogram revealed significant localized stenosis of the main trunk of the middle cerebral artery about one inch from its origin (Fig. 3). There were no definite abnormalities elsewhere in the arteriogram.

COMMENT

Histologic proof of the nature of the partial occlusions in each of these cases is lacking. There is, however, nothing to suggest that these arteriographic ab-

normalities were due to "spasm" from a ruptured aneurysm (Fig. 4) or other intracranial hemorrhage (Fig. 5). The rarely documented occurrence of localized arterial narrowing during a migraine attack (7) or following embolization (8) does not seem applicable to these cases. Congenital narrowing of the involved arteries also seems unlikely. In all probability, the narrowings were arteriosclerotic in nature and they are offered as examples of "segmental" occlusions in unusual sites.

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Factors Determining Chronicity of Liver Disease

A Progress Report

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The investigation of the relation of hepatic injury to hepatic fibrosis was continued with the emphasis shifting towards recognition of the factors which determine the chronicity of liver disease. In general, the techniques applied in the past year (1) such as clinical-pathologic correlation, conventional microscopy, histochemistry, electron microscopy and electron histochemistry, and immunocytochemistry, were supplemented by other immunologic techniques, autoradiography and chemical pathology. In continuation of past work, studies were carried out on material from patients with various liver diseases obtained at autopsy or by biopsy, and in experimental models which were similar to those used in previous years. New models of immunologically induced hepatic injury were added. In the course of this investigation, two aspects of the initial hepatic injury were studied, with different implications for chronicity, namely, the injury of the organelles responsible for specific synthetic functions and energy provision, endoplasmic reticulum and mitochondria, and the injury to the bile secretory and transport mechanism involving canalicular plasma membrane, Golgi apparatus and lysosomes. Functional and structural alterations of the biliary passages were separated into those of the intrahepatic bile duct system and those of the bile ductules. Bile ductular reaction is frequently associated with portal inflammatory reaction and therefore both were considered as a unit. Although the reaction of the hepatic mesenchyma, particularly of the sinusoidal cells, and hepatic fiber formation are part of the alterations described, they are discussed separately as is the mechanism of cirrhosis formation investigated in experimental animals and man. The investigations reported were carried out under the sponsorship of the U.S. Army Medical Research and Development Command Contract DA-49-007-MD-790 and were also to a great extent supported by U.S. Public Health Service Research Grant A-3846 as well as U.S.P.H.S. Training Grant 2G-115 for Experimental Pathology since many postdoctoral trainees and medical students supported by these grants worked on many of the problems discussed. In view of the extensive dovetailing of all the problems involved, a sharp separation of the support by the respective grants is neither possible nor desirable. It was also not possible, during these studies, to separate investigation from training and research which mutually benefited each other.

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ACUTE INJURY OF HEPATOCELLULAR SYNTHESIZING AND ENERGY PROVIDING APPARATUS

Alterations of the endoplasmic reticulum as the site of protein and sterol synthesis, of blood sugar formation and of detoxification, and alterations of the mitochondria were studied in acute and subacute ethionine intoxication in rats and in human viral hepatitis and alcoholic hepatitis.

A. *Ethionine Intoxication of the Rat.* To correlate histochemical and electron microscopic parameters with cytochemical ones, the fine structural appearance of the liver cell was correlated with the chemically determined activity of oxidative enzymes (proline oxidase or succinic dehydrogenase), glucose-6-phosphatase, glutamic pyruvic transaminase and ATPase as well as with the histochemical distribution of acid and alkaline phosphatases, ATPase and 5-nucleotidase (2). In the liver of rats fed a synthetic diet containing 0.5 per cent ethionine for seven days, glucose-6-phosphatase, glutamic-pyruvic transaminase and ATPase were normal, while the endoplasmic reticulum was severely disrupted and many "myelin profiles" were seen. At this time moderate swelling of mitochondria coincided with decreased activity of oxidative enzymes. After seven weeks on the diet, increased mitochondrial distortion was associated with further drop in activity of oxidative enzymes. The endoplasmic reticulum was more severely altered while glucose-6-phosphatase activity was decreased. ATPase activity around bile canaliculi was decreased but was increased around ductular cells. The total ATPase activity determined chemically was increased. These studies indicate simultaneous injury of endoplasmic reticulum and mitochondria with good correlation between mitochondrial structure and function. The correlation of the structural and functional parameters of the endoplasmic reticulum was unsatisfactory.

B. *The Effect of Steroids on Cytoplasmic Organelles.* The studies on ethionine intoxication were extended to include the effect of cortisone (3). Cortisone administration during the florid phase of the intoxication protected or restored the alterations of the endoplasmic reticulum and mitochondria similarly to methionine. The existence of florid and stationary stages was recognized (4). Cortisone arrested but did not reverse the progression of the lesion to the florid stage and restored decreased enzyme activity to normal. In the stationary phase in which an anabolic-catabolic equilibrium seemed to be present, cortisone had no effect.

C. *Viral Hepatitis.* Electron microscopy of biopsy specimens at various stages of viral hepatitis revealed alterations of the endoplasmic reticulum with transformation from ribosome lined to smooth ergastoplasm, disruption of the profiles to form vesicles, and in some instances swelling of mitochondria. Clumps of ribosomes were found free and not attached to membranes. Variation of organelle changes from cell to cell confirm light microscopic observations (5). It appears thus that basically in viral hepatitis, the organelles of synthesis and energy provision are involved.

D. *Alcoholic Hepatitis.* The changes occurring in patients with alcoholic induced hepatic injury were reviewed (6), and a series of those admitted because of jaundice and hepatocellular failure ascribed to acute alcoholic hepatitis were

studied by electron microscopy (7). The chief cytoplasmic alteration was enlargement and clumping of hepatocellular mitochondria and this was thought to represent Mallory's alcoholic hyaline. The mitochondrial matrix was not less dense than normal and hence the lesion was not the result of simple swelling. Gigantic and often bizarre mitochondria were found. The endoplasmic reticulum was often intact although in cells with large fat droplets the amount of all organelles was reduced.

DISTURBANCE OF BILE SECRETORY AND TRANSPORT MECHANISM OF LIVER CELL

A. *Hepatocellular Acid Phosphatase.* Acid phosphatase distribution in various diseases and experimental conditions was studied in which alteration of lysosomes and of the acid phosphatase containing granules seem to play a role and in which pigment deposition or finally cholestasis was recognized. To analyze further the role of the acid phosphatase containing organelles, more reliable histochemical techniques were developed. A simultaneous coupling azo dye method, using naphthol AS-TR and AS-BI phosphates with hexazonium pararosanilin as coupler gave artefact-free localization of enzyme activity in formol calcium fixed frozen sections. A survey of various tissues using this technique revealed an almost universal occurrence of acid phosphomonoesterases. The variation of enzyme activity in different locations indicated a parallelism between the development of the pinocytotic and reversed pinocytotic apparatus of the cell and its acid phosphatase content. The increase of enzyme activity and spreading of enzyme-containing granules observed in various forms of liver injury were interpreted as a compensatory increase of pinocytotic activity as contrasted to active cell membrane transport mechanism. The acid phosphatases of liver constitute a family of related enzymes. Using polyacrylamide gel electrophoresis and anion exchange cellulose chromatography, four distinct acid phosphomonoesterase fractions could be resolved (8, 9).

B. Lysosomes as Organelles for Storage, Breakdown or Excretion. Histochemically the lysosomes are defined as acid phosphatase containing and usually PAS positive bodies. Electron microscopically they are recognized as single membrane enveloped structures containing irregularly arranged material of variable electron opacity. They differ from microbodies with central nucleoid. Improvement of the identification of lysosomes by electron histochemical demonstration of acid phosphatase is in progress. The development of hepatocellular vacuoles was studied in anoxic rats. The pinocytic origin of these was demonstrated by their content of colloidal mercuric sulfide following its intravenous injection (10). The vacuoles became smaller the closer they were to the bile canaliculus, indicating loss of fluid. In the pericanalicular zone, single membrane lysosome-like structures were seen which contained mercuric sulfide. Increased numbers of lysosome-like structures were found after repeated intravenous injection of fat (11). Another type of membrane enclosed body containing cellular breakdown products such as degenerated mitochondria, described as cytolysosomes, was found more frequently in the livers of anoxic animals, reflecting increased turnover of individual organelles in viable liver cells. It thus appears that the lysosome is a device for isolating material entering the liver cells by pinocytosis

or formed by intracellular breakdown. The distribution of the acid phosphatase containing granules resembles that of the PAS positive granules which presumably contain glycolipoprotein. However, the acid phosphatase reaction is far more sensitive than the PAS reaction. The role of the glycolipoprotein as a constituent of the matrix of the lysosome and its origin from the plasma membrane or other cell constituents and its function as an ion exchange resin is under consideration.

C. *Hepatic Giant Cells.* Increased organelle turnover, reflected in many cytolysosomes, is particularly frequent in giant cells in infancy, which occur not only in giant cell hepatitis but also in various forms of biliary atresia. These cytolysosomes in giant cells and usually also in accompanying parenchymal cells gave intense acid phosphatase and PAS reactions. Endoplasmic reticulum and mitochondria showed no significant changes.

D. *Wilson's Disease.* Alteration of the lysosomes was also a crucial feature in Wilson's disease in which a postnecrotic type of cirrhosis is associated with light microscopic alterations of the liver cells. These changes were glycogen degeneration of hepatic nuclei, fine cytoplasmic fat droplets, and accumulation of lipofuscin pigment (12). These features in young non-diabetic persons with or without cirrhosis were considered suggestive of Wilson's disease. Electron microscopically increase in number and density of lysosomes was seen whereas histochemically the acid phosphatase reaction of the liver cells was reduced in contrast to increased activity in neighboring sinusoidal cells. This was considered the result of interference with acid phosphatase activity by copper. The fine structural alterations were considered diagnostic and particularly helpful in asymptomatic patients (13).

E. *Cholestasis.* Spotty dilatation of the bile canaliculi was found in liver biopsy specimens from patients with extrahepatic and intrahepatic cholestasis and in livers of rats after ligation of the common duct or following administration of anabolic steroids. In these conditions at least three hepatocellular organelles, biliary canaliculi, Golgi apparatus and lysosomes were involved. The participation of the last was indicated by the increased acid phosphatase activity in cholestasis with spreading of the granules through the liver cells and by the accumulation of acid phosphatase around stagnating bile.

F. *Acid Phosphatase and Biliary Excretion.* The close topographic relation of acid phosphatase containing bodies to the bile canaliculi suggested the possible role of these granules in bile excretion. Acid phosphatase activity was demonstrated in rat bile. Dilution experiments indicated that the true acid phosphatase activity of bile was probably higher than measured since the enzyme was inhibited by some non-dialyzable constituents of bile, probably bilirubin. Acid phosphatase activities of bile and serum showed no correlation. A direct correlation was found, however, between acid phosphatase activity and bilirubin concentration in bile in both normal animals and in rats in which hydrocholeresis was produced by Decholin Sodium®. During hydrocholeresis acid phosphatase activity of bile was reduced, while after injection of bilirubin it was increased.

G. *Bile Secretory Apparatus.* Involvement of the Golgi apparatus in cholesta-

sis was reflected in the deposition of electron opaque material within dilated vesicles. The participation of the bile canaliculus has received most of our attention (14–16). In both intrahepatic and extrahepatic cholestasis, the microvilli were stunted, swollen or absent. The changes of the bile secretory apparatus were not equal in neighboring cells with cytoplasmic constituents altered in some and canaliculi in others. This explains the irregular dilatation of the canaliculi in all types of cholestasis. The irregular involvement of neighboring cells and the centrolobular localization of bile stasis in extrahepatic biliary obstruction indicate that simple hydromechanical factors are not solely responsible for cholestasis. Rather a specific defect of the bile secretory apparatus, which is identical with that occurring in intrahepatic central cholestasis, has to be assumed. The extent of the central cholestasis does not parallel the degree of injury to endoplasmic reticulum and mitochondria. These conclusions were supported by the analysis of a large number of drug induced hepatic injuries which had been analyzed by various methods and classified (17).

BILE DUCTULAR REACTION

The study of the proliferation of bile ductules usually associated with inflammatory reaction was continued (18). Proliferation of bile ductules was associated with fibrosis. It was also related to immunologic processes but not to the development of cancer. The proliferation of bile ductules was associated with hydrocholeresis. Both proliferation and the accompanying reactions were influenced by steroids. The hypothesis was presented that the bile ductular proliferation serves in the perpetuation of liver disease by spreading injurious substances throughout the liver. In addition to proliferation, electron microscopic evidence was obtained for significant alterations of ductules in the bile ductular reaction. Furthermore, suggestive evidence was obtained for destruction of ductules. These changes may result in regurgitation of bile through altered ductules. Also, compression and possible destruction of ductules may produce mechanical intrahepatic cholestasis. This is conspicuous in more advanced stages of primary biliary cirrhosis and is also seen in subacute stages of viral hepatitis.

INJURY OF BILE DUCTS

Damage to the bile secretory mechanism of the liver cells in central intrahepatic cholestasis, and to bile ductules causing either obstruction or local regurgitation, was considered responsible for elevated levels of conjugated bilirubin. A third factor was injury to the intrahepatic bile ducts resulting in regurgitation. The prototype of this lesion was alpha-naphthyl-isothiocyanate intoxication. Israeli investigators demonstrated the development of transient severe jaundice soon after administration of this drug and associated it with alteration of the interlobular bile ducts. In continuation of these studies (19), complete cessation of the bile flow coincided with destruction of lining epithelium of the ducts or with inflammatory swelling of their wall. Since under these circumstances no evidence of bile stasis or bile canalicular alteration was noted

by light microscopy, histochemically or by electron microscopy, this supported the hypothesis that the jaundice was caused by regurgitation through the bile ducts rather than cholestasis. Necrosis around bile ducts is probably also caused by regurgitation.

Similar but less severe alterations of bile ducts were occasionally found in drug induced hepatic injury (20). Bile duct lesions encountered early in the course of primary biliary cirrhosis in the absence of central cholestasis or significant bile ductular proliferation pointed to the bile duct as the initial site of injury in this condition (21). This and the fact that the bile canaliculi were normal even in the presence of jaundice suggested that the initial insult is to the bile ducts. Canaliculi were abnormal only after anabolic steroids were given in the treatment of itching. Based on examination of many cases of primary biliary cirrhosis (22), three stages were distinguished: 1) injury to bile ducts, 2) proliferation of the bile ductules with periductular inflammation, and 3) destruction of ductules with replacement by connective tissue. In the latter two stages, peripheral bile stasis is noted. Primary biliary cirrhosis thus appears to differ from the common drug induced hepatic injuries where central cholestasis is usual. The presence of immunologically competent cells containing macroglobulins around the altered bile ducts in the earlier stages suggested an immunologic mechanism in the pathogenesis of primary biliary cirrhosis. This is supported by the demonstration of macroglobulins and rheumatoid factors in the serum of such patients. Since some patients with primary biliary cirrhosis have a history of biliary tract disease or of viral hepatitis, and since macroglobulin containing cells were also occasionally found in secondary biliary cirrhosis, it is postulated that primary biliary cirrhosis represents a peculiar immunologic reaction which may be precipitated by any injury to bile ducts.

REACTION OF HEPATIC MESENCHYMA

In view of the role of hepatic mesenchyma in chronic liver disease and cirrhosis, mesenchymal cells and tissue spaces were studied by ultrastructural, histochemical and immunocytochemical techniques (23). In addition to hematic cells, five cell types were identified in the parenchyma either in a littoral position or in the tissue spaces: 1) an endothelial lining cell or resting histiocyte, 2) a phagocytic cell containing many phagosomes which corresponded to Kupffer cells when in a littoral position, 3) a fiber forming cell, 4) a protein forming cell with abundant endoplasmic reticulum, and 5) a cell which contained phagosomes with fluorescent lipofuscin indicating phagocytic ability and with extensive endoplasmic reticulum with ribosomes in another portion. They also exhibited fluorescence when treated with tagged anti-gamma globulin. A particular role in the immune processes was ascribed to the last two groups of cells (24). This division of hepatic mesenchymal cells does not necessarily indicate postembryonal derivation from a single precursor reticulum cell. They could be the result of proliferation of different cell lines as the result of stimulation. While proliferation of endothelial and phagocytic cells is in the foreground

in conditions with acute injury to hepatic cells, protein forming and fibroblastic cells were prominent in chronic damage. Hypergammaglobulinemia and various immunologic reactions were related to increased activation of the mesenchyma. When serum proteins from patients with cirrhosis were separated electrophoretically on polyacrylamide gel, the increased gamma globulin with reduced haptoglobulins and alpha and beta glycoproteins resulted in a smudged appearance of the slower moving portion of the electrophoretic pattern rather than normal sharp bands (25). The mesenchymal reaction within the parenchyma also reduced effective hepatic blood flow by causing changes in the sinusoidal endothelial lining and the space of Disse (26). The space widens in acute hepatic injury. The endothelial lining is separated from the liver cell plate by electron transparent material, presumably edema fluid with some cellular debris. This morphologic change may be associated with leakage of enzymes from the hepatocytes. When injury is protracted, the sinusoidal lining becomes more than one cell thick. Fiber bundles formed in the space of Disse may eventually be a barrier to blood liver cell exchange. A basement membrane develops later, converting the sinusoids into capillaries and transforming an open hepatic circulation into a closed one, further reducing effective hepatic blood flow. This provides an added explanation for hepatic insufficiency in cirrhosis.

HEPATIC FIBROSIS

Recent studies of hepatic fibrosis centered around the mechanism of formation and removal of collagen fibers.

A. *Carbon Tetrachloride Intoxication.* In continuation of studies on ethionine intoxication as an example of periductular fibrosis (27), the chronic carbon tetrachloride intoxication was investigated initially in the attempt to study a perihepatocellular type of fibrosis. In this investigation which combined histologic, chemical and autoradiographic techniques (28), the evolution of the carbon tetrachloride induced cirrhosis was divided into four stages: 1) necrosis, 2) nonseptal fibrosis, 3) septal fibrosis, and 4) cirrhosis. During the first stage central fiber accumulation was not accompanied by an increase of hepatic hydroxyproline as a measure of collagen. This indicates that this central fiber aggregation results from collapse rather than from fibrogenesis. Subsequently the hydroxyproline content rose progressively during the duration of the experiment. Hepatic DNA content as a measure of cells rose parallel during the period of nonseptal fibrosis while subsequently the increase of the hydroxyproline far exceeded that of DNA. It appears that in the initial period of new fiber formation, cells increased parallel to fibers. When septal fibrosis and cirrhosis formation started, fiber accumulation was greater than that of cells because of more effective production of collagen by individual cells or because of decreased turnover of previously formed collagen. This basic difference between nonseptal and septal fibrosis may be related to the reversibility of the lesion. During the stage of necrosis, a striking number of labelled hepatocytes were seen in autoradiographs accompanied by a similar increase in labelled

mesenchymal cells. At this time the total thymidine uptake by the liver was greatly elevated. The response to carbon tetrachloride differs from that to hepatectomy since the proliferation of mesenchymal cells associated with necrosis reflects a hepatitis. This explains the histologic similarities between toxic hepatic necrosis and viral hepatitis and accounts for difficulties in differential diagnosis. During the stage of nonseptal fibrosis, the total thymidine uptake drops almost to control levels.

The subsequent onset of septal fibrogenesis is associated with another peak of thymidine uptake and autoradiographs indicate that proliferating ductular cells and hepatocytes in developing nodules were responsible. In contrast, in the well-developed nodules, uptake of tritiated thymidine was reduced despite architectural evidence of regeneration. This suggested increased life span of hepatocytes in nodules. The topographical and temporal relations between ductular cell proliferation and septal fibrogenesis point to the significance of periductular fibrogenesis in carbon tetrachloride cirrhosis and possibly also in human cirrhosis.

B. *Ethionine Intoxication.* Ethionine induced hepatic fibrosis is completely reversible after substitution of methionine for ethionine. Much collagen and many ductular cells disappear from the liver within 15 to 20 days. The mechanism of this phenomenon was studied with radioisotope techniques (29). In spite of the rapid disappearance, the life span of thymidine-H^3 labelled ductular cells was similar in fibrotic livers and during recovery. This indicated that the inhibition of renewal of these cells during recovery and not more rapid catabolism accounted for their disappearance. In contrast the half life of hepatic collagen was considerably reduced and its turnover rate increased. The specific activity of the alkali soluble collagen labelled with proline C-14 had a short half life in both fibrotic and recovery groups but a second peak of activity developed in this fraction ten days after the institution of recovery. The source of this increased activity was the insoluble collagen becoming soluble, suggesting breaking of interchain linkage and depolymerization of the collagen. This was further confirmed by the demonstration of increased susceptibility of hepatic collagen to collagenase and to trypsin digestion during recovery and the possible weakening of mucopolysaccharide complexes. Disappearance of the ductular cell as the framework owing to lack of renewal seemed to facilitate depolymerization of collagen and to increase susceptibility to proteolytic enzymes and to phagocytosis by mesenchymal cells. Other types of fiber formation were investigated (30, 31).

C. *Cirrhosis.* The study of different types of cirrhosis by various techniques was continued. Postnecrotic cirrhosis in alcoholics was further evaluated (32). Fibrosis and cirrhosis formation was also studied in schistosomiasis (33, 34).

As part of the study of the effect of carcinogenic agents on the liver (35), groups of rats were fed different hepatotoxic agents and sacrificed at intervals to correlate patterns of injury, fibrosis and regeneration with formation of cirrhosis. Septal cirrhosis, in which fibrous septa are thin and portal tracts are not approximated by collapse, was produced in two ways: 1) With passive

nodule formation in thioacetamide intoxicated rats and in those fed a choline deficient diet. Zones of injury and necrosis showing owl-eyed cells in thioacetamide fed rats and fatty cysts in choline deficient rats linked central veins to each other and to portal tracts. Ductular cell proliferation and new septa formation along these zones ultimately divided the parenchyma in a monolobular fashion. 2) With active nodule formation in rats intoxicated with methyl butter yellow in which intralobular necrosis was more severe. In the livers of these animals, regenerating foci around portal tracts gradually enlarged, compressed adjacent parenchyma and produced septa on their peripheries.

Postnecrotic cirrhosis, characterized by approximation of portal tracts and central veins, by broad scars and by nodules with preserved architecture or hyper-regenerative features, was seen in rats intoxicated with thioacetamide for long periods. The initial septal cirrhosis progressed in a manner suggested for human postnecrotic cirrhosis. Rapidly growing foci appeared in the nodular centers, gradually enlarged, and caused continuing compression and thick septa formation at the nodular periphery. As these nodules enlarged, a nearly normal appearing architecture frequently resulted from relobulization in which blood vessels and bile ducts grew in from the nodular periphery. Multilobular nodules thus can develop from small groups of liver cells.

IMMUNOLOGIC HEPATIC INJURY

Investigations of past years (36, 37) were continued to demonstrate: 1) formation of gamma globulin, possibly antibodies, in the liver and its relation to the morphologic alterations, 2) presence of antigens within liver, and 3) the possibility of producing experimental hepatic injury. Persistent hepatic injury independent of the initial etiology as characterized by "piecemeal necrosis" was associated with local formation of gamma globulin (38). The loss of liver cells was accompanied by accumulation of lymphocytes, plasma cells, histiocytes and proliferation of bile ductules. In contrast the biliary cirrhosis syndrome characterized by accumulation of lymphoid cells forming macroglobulins around bile ducts and ductules may be caused by specific cytotoxic antibodies directed against ductules and ducts (39). Otherwise, macroglobulins were only demonstrated in the liver of a patient with Waldenstroem's macroglobulinemia complicated by subacute hepatitis (40).

Antigenic material in the liver was investigated in schistosomiasis as a useful model with known antigen (41). The serum of patients with active liver disease, particularly chronic active hepatitis and primary biliary cirrhosis, contained a high level of substances binding ductules and nuclei as shown by immunofluorescence. Further evidence of the antibody nature of these substances was obtained using an immunocytochemical demonstration of complement fixation (42).

Among the various attempts to produce hepatic injury by immunologic techniques, those which resulted in piecemeal necrosis were considered particularly significant in view of the possibility that piecemeal necrosis represents an immunologic insult, possibly with local deposition or formation of antigen-antibody complexes. To investigate the response of the liver to antigen-antibody

complexes in and around bile ducts, soluble immune complexes (horse serum-anti horse serum and bovine albumin-anti bovine albumin) were injected into the bile ducts of rats (43). The complexes were retained in the bile duct lumen longer than their components and subsequently portal inflammation and periportal hepatocellular necrosis developed with localization of the complexes in macrophages, necrotic areas, connective tissue and vessels. Portal inflammation followed by fibrosis persisted for at least one week. It was concluded that an immunologically induced tissue damage in the liver need result neither from circulating antibodies nor cell bound immunity directed against components of liver tissue, but may be induced by the local formation or deposition of antigen-antibody complexes with subsequent cytotoxic effects.

In carbon tetrachloride and allylalchohol intoxicated mice, the cells of the reticuloendothelial system, particularly in spleen and portal lymph nodes, were activated. In these locations many gamma globulin containing cells were seen. The activation of the reticuloendothelial system coincided with high serum gamma globulin levels. Extensive piecemeal necrosis progressing to cirrhosis was noted in animals after a single intravenous injection of silica. Subsequent studies of the production of antibodies in such animals revealed an adjuvant effect of the silica related to proliferation of immunologically competent cells (44). The longer the interval between silica and antigen injection, the higher the antibody titer. Antigen-antibody complexes were detected in several organs.

Other experimental models of immunologic induced hepatic injury included severe piecemeal necrosis in rejection of homotransplanted dog liver and carbon tetrachloride induced hepatic injury by simultaneous continuous antigenic stimulation. This resulted in severe piecemeal necrosis progressing to diffuse postnecrotic cirrhosis with many mesenchymal and immunologically competent cells. Antigen-antibody complexes localized in this lesion were responsible for the aggravation of the injury.

In conclusion, evidence was obtained for the production by the diseased liver and reticuloendothelial system of antibody to ductular cells or nuclei, and for the local cytotoxic effect of antigen-antibody complexes. Finally, immunologic models are now available for the study of piecemeal necrosis, its relationship to immunologic processes and the role of immune reactions in the perpetuation of liver disease.

SUMMARY

The emphasis of the investigation of acute hepatic injury and processes leading to cirrhosis shifted to recognition of the factors determining chronicity, particularly fiber formation and immunologic hepatic injury. Acute hepatic injury was subdivided into alerations of the hepatocellular synthesizing and energy providing apparatus and those of the bile secretory and transport mechanism. Disturbances of the former characterize specific liver diseases with endoplasmic reticulum functionally and structurally more involved in viral hepatitis and with mitochondria more involved in alcoholic hepatitis. Cholestasis is caused by arrest of bile production and flow at different levels of the

bile secretory apparatus consisting of canaliculi, Golgi apparatus and lysosomes. The contribution of the last in bile secretion was demonstrated by studies of hepatic and biliary acid phosphatases. Specific injury of the bile ducts leading to regurgitation was demonstrated in primary biliary cirrhosis. In studying the reactions of the hepatic mesenchyma, phagocytic and protein forming cells were separated and transformation of the open circulation into closed in cirrhosis was demonstrated. Study of experimental models indicated that much of the hepatic fibrosis was related to rapid proliferation of bile ductules. Their disappearance facilitated removal of fibers which were depolymerized and became more susceptible to proteolytic enzymes and to phagocytes. In the immunologic study of liver diseases, hepatic formation of gamma globulin and specific circulating antibodies to liver were demonstrated. Several experimental models of hepatic injury were produced, presenting the "piecemeal necrosis" characteristics of the self-perpetuation in human cirrhosis. In these models, either the effect of specific anti-liver tissue antibodies or cytotoxic injury from nonspecific antigen-antibody complexes may be the significant pathogenetic factor.

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CLINICO-PATHOLOGICAL CONFERENCE

Jaundice, Ascites and Corneal Discoloration with Normal Ceruloplasmin

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A 28 year old, New York born, handyman of Puerto Rican parentage, was admitted to The Mount Sinai Hospital for the first time because of increasing abdominal swelling for one week. About a month before admission, he developed anorexia and malaise, was occasionally nauseated and vomited a few times. At this time his urine became dark and his stools light. He also lost his taste for cigarettes. His abdomen gradually began to swell but he had no pain or fever. Two days later his eyes became yellow and he noted increased weakness and lethargy. On the day of admission he had diarrhea nine or ten times. He had been drinking beer and five to six ounces of whiskey a day since the age of 15 years although recently most of the drinking was on weekends. He was married and had three children. He had never been outside the United States. He had not been exposed to solvents or any other toxic substances. The only previous serious illness was bronchopneumonia at the age of seven years.

The patient had three siblings 25 to 30 years old who were alive and well. His mother died at age 34 of heart disease but his father was alive and well. His maternal grandmother, still alive, was said to have liver and heart disease. Three of his children were well and a fourth died of leukemia in infancy.

The patient was well developed but acutely ill and lethargic. His temperature was 100°, pulse 120/min and regular, and blood pressure 150/80. The sclerae were icteric and a greenish-brown discoloration was seen at the limbus of the cornea although the patient was brown-eyed. On slit lamp examination this was a uniform discoloration of Descemet's membrane characteristic of a Kayser-Fleischer ring. Slit lamp examinations of several of the patient's relatives were negative. The heart and lungs were normal. The abdomen was distended and tense with shifting dullness and no organs could be felt. Edema, clubbing, spider angiomata, palmar erythema, asterixis, testicular atrophy, abnormal body hair distribution, tremor, rigidity, dysarthria and abnormal involuntary movements were absent. Neurological examination was normal except for lethargy.

The urine specific gravity was between 1.010 and 1.046. The urine was persistently acid and neither albumin nor sugar was found. A few red and white blood cells were occasionally noted. The Sulkowitch reaction was 2+. Urinary sodium was 22 mEq/l, potassium 36 mEq/l, and chlorides 30 mEq/l. Over a two-week period on a Bauer-Aub diet, daily urinary calcium excretion averaged 212 mg with a range of 130–269 mg, daily phosphate excretion averaged

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1017 mg with a range of 630–1531 mg while uric acid excretion was 630 mg/day with a range of 250–972 mg. Urinary copper was 2.5 mg/day (normal less than 0.1 mg). Hemoglobin was 10.4–12.0 Gm% with a hematocrit of 38%. The initial white blood count was 7,800/mm³. This gradually rose to 16,000/mm³ before death. Differential counts showed 7–8% band forms, 6–7% monocytes, and 8% eosinophiles on one occasion. Sedimentation rates were 55–70 mm/hr. Prothrombin time was 18–32 sec with a control of 12 sec despite vitamin K therapy. A non-gamma Coombs test was negative as were several blood cultures. Serum haptoglobulin was 12 mg% and serum ceruloplasmin 25 mg%. BUN was 10–17 mg%, creatinine 0.4–0.9 mg%, uric acid 0.9–1.0 mg%, and ammonia 1.8–2.6 mg/ml. Uric acid determinations on several other family members were normal. Serum electrolytes were normal on admission but terminally sodium fell as low as 112 mEq/l and chlorides to 75 mEq/l. Serum calcium was 8.1–9.1 mg% and phosphorus 2.0–2.5 mg%. Blood sugar was normal. Serum albumin was 1.3–2.3 Gm% and globulin 4.7–6.3 Gm% while electrophoresis showed depression of all fractions except gamma globulin which was greatly elevated. Serum bilirubin was 3.8–16.0 mg with 2.1–9.0 mg% direct reacting. The high values developed in the last two weeks of life. Thymol turbidity was 5.2–6.6 units, cephalin flocculation 2–3+, transaminase 108 units on admission, dropping to a low of 80 units and rising terminally to 218 units. Serum cholesterol was 90–135 mg% with 85–110 mg% esters. Serum alkaline phosphatase was 4.7–10.6 King-Armstrong Units and acid phosphatase 5.2 King-Armstrong Units. Stools contained no ova, parasites or pathogenic bacteria and initially were guaiac negative although in the last week of life all stools gave a 2–4+ guaiac reaction. Ascitic fluid had a specific gravity of 1.010, contained 50 cells mainly lymphocytes and 1.4 Gm/l protein. Cultures were negative. Spinal fluid was clear under normal pressure, and contained no cells, 67 mg% sugar, 127 mEq/l chlorides and 16 mg% protein. Serology was negative and a gold curve was 2221100000. An electroencephalogram and electrocardiogram were normal. Chest x-ray showed elevated diaphragms and an abdominal film indicated ascites. A bone survey was negative and varices were seen on a barium swallow.

The patient was treated with protein and salt restriction, fluid and vitamins. His lethargy cleared quickly, and he became afebrile but he did not lose any of his ascitic fluid. Neurological examination was repeatedly normal. After 24 days of rest and observation, he was started on chlorothiazide and spironolactone and lost 32 pounds in four days. At that time he developed hematemesis, epistaxis and gingival bleeding. The diuretics were stopped and the patient given neomycin, enemas and antacids. Despite this he became lethargic and obtunded over the next ten days. Asterixis was noted, jaundice rapidly increased and ascites quickly reaccumulated. On the 38th hospital day, he had a massive hematemesis and died within the hour.

Dr. I. Herbert Scheinberg:* This is not going to be a problem in making a diagnosis but it probably will be an exercise in justifying a diagnosis.

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I think this patient had Wilson's disease because he had Kayser-Fleischer rings and I know of no other condition that gives rise to these except the presence of intra-ocular foreign bodies of copper.

Further, the severe liver disease, which killed him, must have been due either to Wilson's disease or to hepatic cirrhosis due to another cause such as hepatitis. Although of Puerto Rican extraction, he was New York born, and I do not think we seriously have to consider parasitic disease.

Is there further evidence, in addition to the Kayser-Fleischer rings and the liver disease, that he had Wilson's disease? There is a little in the uric acid clearance. The normal clearance of urate is 8 ml/min; in Wilson's disease it has been found to be elevated (values from 14–32 ml/min have been reported), and in this patient it was 44 ml/min. In Wilson's disease there is impairment in the reabsorption of urate so that there is a greater clearance with somewhat lowered levels of serum uric acid, as there was here. These abnormalities in uric acid metabolism are not, by the way, consistently found in Wilson's disease.

The finding which is unusual for this diagnosis is a serum ceruloplasmin of 22–35 mg%. Ceruloplasmin is a blue serum protein which has been thought by a number of investigators to play some role in the pathogenesis of Wilson's disease (1). The concentration of this protein in most normal individuals is 20–35 mg%. In 96 per cent of 110 patients with Wilson's disease, levels of ceruloplasmin were below 20 mg%, and ninety per cent had a level below 15 mg%. We saw four patients whose ceruloplasmin concentrations were in the same range as in this patient.

If this is a hereditary disease, as everybody believes, and if this protein is the primary gene product, or closely related to it, we should not find *bona fide* cases where the concentration of ceruloplasmin is normal any more than we should find patients with a gammaglobulinemia who have normal concentrations of gamma globulins. Yet the low concentration of serum ceruloplasmin in a patient with Wilson's disease can rise to within the normal range in at least three situations.

First, ceruloplasmin levels within the normal range were noted by Drs. J. L. German and A. G. Bearn after these patients were given estrogens (2).

Second, in four patients in whom the concentration of ceruloplasmin was measured before, during and after pregnancy, the concentrations rose from characteristically low to almost normal values and then fell after delivery.

Third, Dr. I. Sternlieb and I have seen or read of ten other patients with Wilson's disease in whom ceruloplasmin levels were normal. All ten had severe liver disease at the time that their relatively high concentrations of ceruloplasmin were found. In two patients there was a subsequent decrease in the ceruloplasmin concentration to the characteristic range. Another two died of hepatic coma, with jaundice, ascites, increased gamma globulin and hepatomegaly.

To summarize, although a low concentration of ceruloplasmin is present in a very large majority of patients with Wilson's disease, some patients may exhibit a normal concentration of the protein at some phase of the disease. This may happen if such a patient is given estrogen, it may happen if she gets

pregnant, or it may happen at the time the patient's liver disease is active or severe. And, if the liver disease improves, the concentration of ceruloplasmin may revert to its usual low normal level.

Is there any way of making sure of the diagnosis if the patient is first seen with a normal concentration of ceruloplasmin, as was true in this case? I think so because patients with Wilson's disease have elevated concentrations of hepatic copper. Indeed, we believe Wilson's disease *is* chronic copper toxicity so an increase in hepatic copper is the fundamental chemical finding of this disorder. In our own experience this can range from about 200 to 3,000 mg/Gm of dry weight. Thus, if you suspect Wilson's disease in a patient because, for example, he has Kayser-Fleischer rings, and you find a normal concentration of ceruloplasmin, you should analyze his liver for copper. Hepatic copper is not significantly elevated in Laennec's cirrhosis, viral hepatitis or other forms of postnecrotic cirrhosis.

Analysis of the liver of this patient at autopsy showed liver copper to be 254 and 422 mg/Gm dry weight in two different specimens. Furthermore, the concentration of copper in his kidney was 386 mg/Gm dry weight whereas the normal concentration of renal copper is about 10 to 14 mg/Gm. Consequently, this patient had a very high concentration of copper in two organs, both of which were clinically affected.

I conclude that this patient had Wilson's disease with hepatic and renal manifestations, without neurologic disease, but with Kayser-Fleischer rings. Wilson in his original description in 1912 said: "... the most curious and most remarkable feature of this familial nervous disease is the constant presence of a profound degree of cirrhosis of the liver (which) does not reveal itself by any symptoms during life (yet) is always found after death" (3). Since then our picture of this disease has changed so that we know that these patients can come to the clinician's attention in any one of at least three ways: roughly a third will come with hepatic manifestations, as this patient did; a third will come to the neurologist with typical basal ganglia disease or, as Sir Francis Walshe described it, with what looks like a combination of multiple sclerosis and Parkinson's disease; and a third will come to the attention of the psychiatrist, or will be found in mental hospitals either with severe neurotic or psychotic disease.

I have not discussed renal disease because to my knowledge the patient never first seeks medical help for this. I suppose if these patients lived long enough with their hepatic or neurologic disease, they might develop renal failure. Dr. Gutman's work with Dr. Bearn and Dr. T. Yü shows that there is a spectrum of renal disease (4). A tubular abnormality is responsible for the aminoaciduria that Drs. Uzman and Denny-Brown first described, and also, presumably, for the uricosuria (5). Later glomerular function is impaired. One can find normal renal function, minor tubular abnormalities, or early renal insufficiency in patients with Wilson's disease.

Suppose this patient had recovered from the episode of hepatic failure. Could anything have been done to remove the copper, and could the underlying liver disease have been expected to improve? The situation is somewhat like

that seen in alcoholism. When a patient with alcoholic cirrhosis and cerebellar degeneration stops drinking liquor, generally his cerebellar disease gets better but his liver disease does not. If copper is removed by pharmacologic means and a low copper diet from a patient with Wilson's disease who has both hepatic and neurologic manifestations, the neurologic disease will also often improve dramatically. But the hepatic disease improves much less regularly and only moderately at best. Hepatic copper content does seem to fall, as we have seen from analyses of liver copper content in serial biopsies from three patients. In two adults, hepatic copper concentration fell from 1560 to 600 and from 361 to 150 mg/Gm dry weight over about a year. There may be concomitant clinical improvement such as Dr. Sherlock has seen in three of her patients. So if this patient had recovered from his acute episode of hepatic failure and bleeding, we might have been able to help him by removing the copper which we believe to be the ultimate pathogenetic agent in this illness.

Dr. Hans Popper:* The diagnosis of Wilson's disease had been made during life by the clinicians. We had a difficult problem to reconcile the anatomic changes with this diagnosis which we did not doubt. Our group has been interested in this problem for years, particularly Dr. P. Anderson (6). We have studied material from Dr. Scheinberg and Dr. Bearn in addition to our own. This constituted a large number of cases with hepatic changes with and without cirrhosis (7). We never understood why a patient with this disease should have postnecrotic cirrhosis. Subsequently, in a combined study between the group of Dr. Scheinberg and our own group, particularly Dr. F. Schaffner and Dr. T. Barka, using electron microscopy and histochemistry, one finding emerged which permitted us to recognize Wilson's disease in the absence of any histologic changes except nonspecific ones such as an accumulation of pigment and glycogen degeneration of nuclei. This was decrease or absence of acid phosphatase activity from the liver cells while the Kupffer cells had increased enzyme activity (8). The theory presented was that copper in liver cells inhibits acid phosphatase activity.

Dr. Anderson examined the brain grossly and there was nothing abnormal. Microscopically there was an increased number of astrocytes. Dr. Anderson pointed out that the nuclei of the astrocytic cells were enlarged and this has been described both in Wilson's disease and in any type of hepatic coma, and we do know from this story that this patient did have hepatic coma.

There were circumscribed, whitish, granular foci in the lung. On microscopic examination they consisted of areas of consolidation containing a large number of bacteria, presumably pneumococci.

The heart was concentrically enlarged and dilated. Microscopically there were two changes. There was some myofibrosis and some acute myocarditis. This type of acute myocarditis is quite typically found in electrolyte disturbances and is not associated with disturbed copper metabolism. Myofibrosis is found in cirrhosis occasionally.

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Grossly the kidneys showed green discoloration. We saw bile casts in large numbers in the distal convoluted tubules (Fig. 1). Biliary nephrosis, or jaundice of the kidney, has no influence on renal function. Inspection of the glomeruli by the routine technique employed failed to reveal any changes. Dr. R. Schiffman in our department dissected this kidney using the Oliver microdissection technique. Changes found supposedly in Wilson's disease when other typical alterations cannot be demonstrated were not seen. Therefore, the only renal changes of any consequence were biliary nephrosis and deposition of a few crystals in the tubules.

In the prostate we saw squamous metaplasia of the epithelium. This is presumed to be the result of estrogenic stimulation. We have morphologic evidence of what may have been responsible for the higher ceruloplasmin level. In the

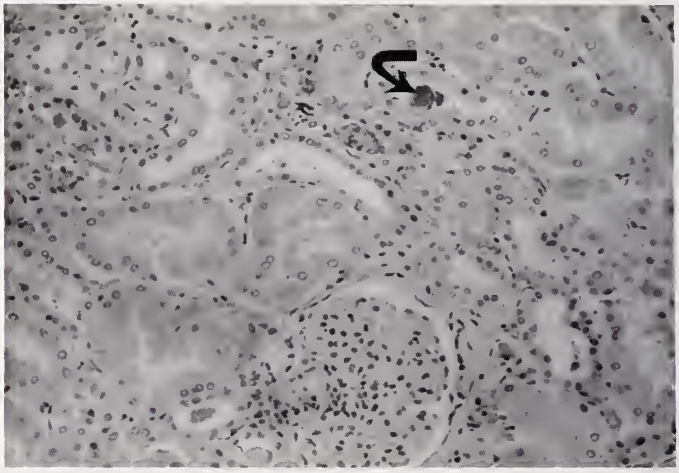

FIG. 1. Section of kidney with normal glomeruli and bile cast in distal convoluted tubule (arrow). (H & E × 40).

testes we found increased connective tissue around the testicular tissues with atrophy and thickening of the basement membrane. This is interesting because this patient was married and had children. I wonder whether this was not recent atrophy and is added evidence of an estrogenic effect.

The stomach was dilated and full of blood. Varices were easily seen. The cause of death in this patient was a very profuse gastrointestinal hemorrhage. The pancreas was entirely normal.

The spleen weighed 360 grams and was enlarged and firm. Microscopically the follicles were somewhat small. We noticed an increased amount of connective tissue and fat in the follicles. Fat here is not diagnostic but it suggested that this patient once may have had necrosis of the liver. Study of sections stained with connective tissue stains showed very recent fibrosis and rather extensive reticuloendothelial hyperplasia with proliferation of the littoral cells and plasma cells in the Billroth cords. This patient had a high serum globin and also many macrocytic cells but the bone marrow and the bones were apparently normal.

The liver was enlarged, weighing 2100 grams. The diagnosis of a fairly coarse nodular cirrhosis was obvious (Fig. 2). On cross section this liver was peculiar. Nodules varying in size from a few to 15 mm in diameter were seen. Most of the nodules were dark green with white tissue between them. The common bile

FIG. 2. Close-up of cross-section showing nodules of varying size and color.

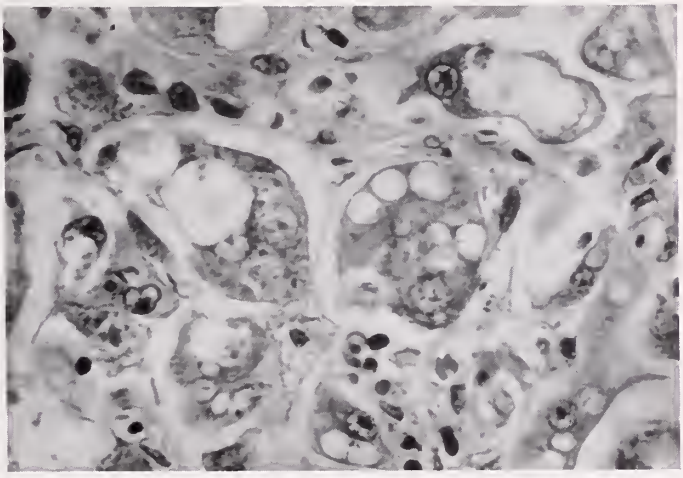

FIG. 3. Large liver cells with multiple vacuoles in their cytoplasm. (H & E × 440).

duct was entirely normal. Two types of nodules were present. One looked fairly typical and the other had parenchymal cells with a somewhat vacuolated appearance (Fig. 3).

The diagnosis by several criteria, namely, multilobular nodules, differential degeneration and broad areas of collapse, was postnecrotic cirrhosis. We were interested in a few features of this postnecrotic cirrhosis. We saw an almost acute atrophy in some lobules, that is, remnants of lobules in which the liver cells

had entirely disappeared. We see that in viral hepatitis, except that there was already increased fibrosis in the connective tissue around the lobule which usually becomes less dense in early collapse.

We were interested in whether collapse was recent or primary collapse of a previously normal liver where the coarse connective tissue bundles of the portal tract are distinct in contrast to the looser collagenous membrane of the stroma of the parenchyma, or whether it was secondary collapse in a cirrhotic liver where the portal tract is rather irregular. In this case we found both collapse of normal tissue and collapse of probably incipient cirrhotic tissue. There was some fat in the portal tracts. This occurs sometimes in a fatty liver after the fat has disappeared from the liver cells. We came to three diagnoses: Wilson's disease, viral hepatitis producing a postnecrotic cirrhosis, and alco-

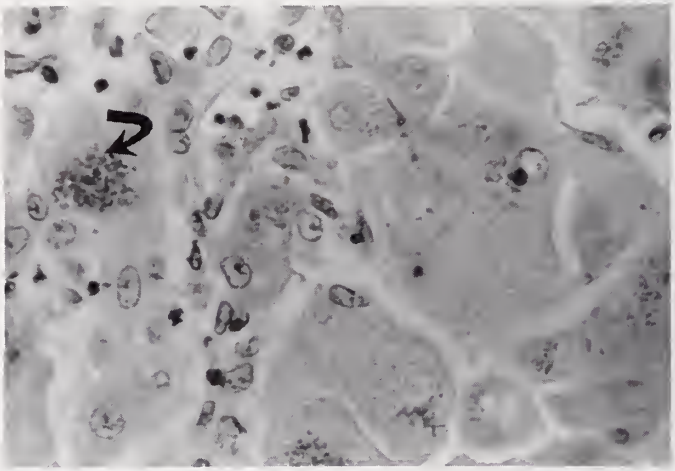

FIG. 4. Granules (arrow) in liver cells with positive hemofuscin and acid fast reactions. (Hemofuscin stain × 440).

holic liver disease with fat. In a few areas of the liver, centrolobular necrosis was seen. This was the result of ischemia probably caused by the recent hemorrhage and was a terminal lesion. We noted a peculiar type of large vacuolated liver cell which we had seen in other cases of Wilson's disease (Fig. 3). They contained little droplets but did not stain like fat. There was pigment in some of these droplets. Very little of it was bile pigment. A few giant cells were also seen which we also noted previously in Wilson's disease. The pigment took the fat stain, as lipofuscin often does. It gave quite clearly a hemofuscin reaction and was also acid fast (Fig. 4). This type of pigment is supposed to be lipofuscin. This particular pigment also contained iron. Acid phosphatase is typically associated with all these pigments, but there was nothing stainable in this case in some areas using Dr. Barka's very elegant and sensitive method for demonstration of acid phosphatase. Where the liver was normal, acid phosphatase in small amounts could be shown, but in the areas where the pigment and vacuoles occurred it was decreased or absent.

Dr. Anderson attempted to make a copper stain. We had never been very

successful previously with the histochemical demonstration of copper, but he succeeded in this case. Copper was in the area with no acid phosphatase activity (Fig. 5). These cells probably disintegrated, leading to collapse and postnecrotic cirrhosis. We would like to consider this peculiar type of cell

FIG. 5. Copper containing pigment in liver cells. (Rubeanic acid reaction × 100).

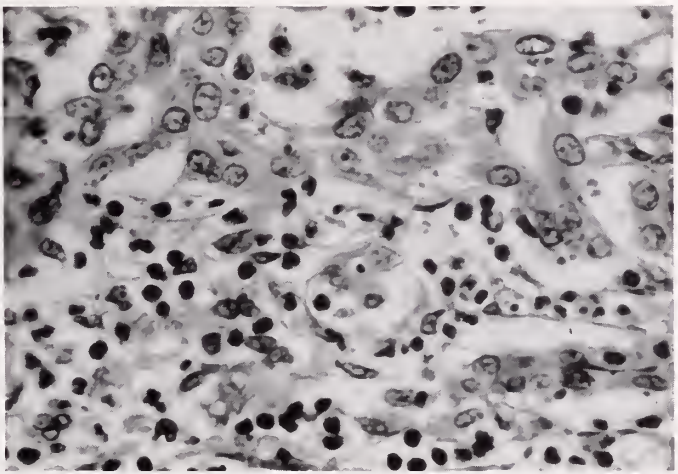

FIG. 6. Leukocytes around proliferating bile ductules but no plasma cells. (H & E × 250).

characteristic of Wilson's disease because we have not seen it in any other condition. The necrotic material gave a PAS reaction which helped in identification. The Kupffer cells contained it and there was a marked proliferation of scavenger cells. This material was also leukotactic. Leukocytes accumulated around the proliferated Kupffer cells. We see this usually in alcoholic hepatitis but we never see such severe reaction around this necrotic material (Fig. 6).

It is now our theory that there is some mechanism in Wilson's disease by which

these cells undergo a specific type of death which in very acute stages leads to a severe reaction which is entirely leukocytic. In the usual type of postnecrotic cirrhosis, plasma cells are seen in this particular periductular inflammatory exudate. Dr. Paronetto examined sections for the presence of gamma globulin containing cells and none were found. Nothing of the kind has been seen by us in Wilson's disease in contrast to other types of cirrhosis which are associated with immunologic processes. There may be antibody formation in other organs, particularly in the spleen, because Dr. F. Paronetto found in the serum of this patient antibody against ductules which we assumed were formed in the spleen as well as in very large lymph nodes found around the liver.

The hepatic vein was the site of a fairly acute phlebitis which caused a marked increase in the portal pressure. This was probably responsible for the terminal ascites for the esophageal varices.

This fairly unusual case may represent a link between the usual type of Wilson's disease and postnecrotic cirrhosis which we have in this instance. We have to diagnose this case as an acute postnecrotic cirrhosis because we saw multilobular nodules, broad areas of collapse, and differential regeneration.

As far as etiology is concerned, we assume that it is most probably Wilson's disease. This is supported by the Kayser-Fleischer rings, the high urinary and liver copper, the presence of glycogen nuclei, and large and vacuolated hepatic cells with decreased activity of acid phosphatase, which may be the result of inhibition by copper. It is tempting to assume that the disturbance of the transport mechanism reflected in decreased acid phosphatase activity is the cause of the hepatocellular enlargement but this is contradicted by the fact that the same enzyme decrease occurs in asymptomatic Wilson's disease. The liver cells disintegrate, eliciting a severe ductular reaction with local and circulating leukocytosis. Antibodies to ductules are formed, with a high serum gamma globulin but with a normal thymol turbidity. Whether alcoholism is a predisposing factor, I cannot decide. Although I think that it is Wilson's disease, I have to raise the possibility that alcoholism plays some role.

In closing, the diagnosis remains anatomically acute postnecrotic cirrhosis of of a very peculiar cytologic type, and a case can be made anatomically to support Wilson's disease.

Dr. Scheinberg: Dr. Popper showed vacuolated cells with peculiar pigment leading to a ductular reaction with leukocytes. Then the antibody formed as part of the reaction perpetuated part of the destruction. I was not sure whether he meant that the vacuolated cells represented all of the necrosis.

Dr. Popper: All except for some acute ischemic necrosis.

Dr. Scheinberg: Therefore, the antibody which was formed might not be the self-perpetuating kind?

Dr. Popper: That is correct.

Dr. Scheinberg: If this man did not have asymptomatic Wilson's disease but had contracted a severe viral hepatitis, then he would not have cells filled with pigment. Is that right?

Dr. Popper: Surely.

Physician: Dr. Scheinberg, you mentioned in the treatment of Wilson's dis-

ease that you saw a response of the neurologic manifestations but usually not of the hepatic ones. What about the psychiatric abnormalities?

Dr. Scheinberg: It is harder to judge this than it is to follow the hepatic and neurologic improvement. I would say that those patients who have had such changes and have been treated have shown improvement.

Physician: Has anybody ever produced any hepatic lesions with copper in animals?

Dr. Scheinberg: Dr. F. B. Mallory, when he tried to prove that Laennec's cirrhosis resulted from copper in liquor, produced cirrhosis in some of the rabbits in whom he injected copper in lard. Subsequently, Drs. Pappenheimer and Von Glahn tried to repeat this and could not. I do not know if anyone has been able to produce cirrhosis by means of copper with the exception of Mallory.

Dr. Popper: John Walshe has a group of ferrets which get a very peculiar liver disease and a peculiar vascular tumor of the liver from copper. I do not know whether it is specific for ferrets or whether it can be duplicated in any of the other animals.

Physician: Dr. Scheinberg, in view of the interesting association of normal serum ceruloplasmin in the few cases that have been reported with apparently severe liver disease, would you comment on the recent paper published by Walshe in Lancet where he showed that ceruloplasmin levels in juvenile cirrhosis were inversely related to severity of liver disease.

Dr. Scheinberg: He described three patients with fatal hepatitis who had a low ceruloplasmin. In one case of chronic hepatitis, a low level returned to normal as the patient improved. I think that if a patient has severe hepatitis with a low serum ceruloplasmin level, one might hesitate to make a diagnosis of Wilson's disease unless hepatic copper was found to be high at the same time, or unless the low ceruloplasmin level persisted after the liver disease improved.

Dr. Alexander B. Gutman:* I would like to close with a comment on the lack of any morphological indications of Wilson's disease in the kidney. In the kidneys of patients with unequivocal Fanconi's syndrome with aminoaciduria examined by electron microscopy and light microscopy, no morphological indications of disease may be seen in the face of severe functional disability. Considerable functional impairment, for instance due to enzyme lack, may be present for quite a while without any structural changes that can be found even with the electron microscope. It has been shown that there is considerable deposition of copper in the kidneys of patients with Wilson's disease with functional impairment and yet even by intensive search by experts, no very obvious structural changes can be shown.

Final Diagnosis: ACUTE POSTNECROTIC CIRRHOSIS IN WILSON'S DISEASE.

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RADIOLOGICAL NOTES

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CASE NO. 209

A 2½ year old child caught her arm in the moving rollers of a power-driven washing machine. Because she was of short stature her arm was drawn into the rollers to the level of the axilla. Her arm was extracted by the release of the rollers. She sustained a typical injury, which on physical examination showed diffuse swelling of the arm and small areas of ecchymosis of the skin. X-ray examination showed extensive soft tissue swelling associated with distortion of the normal tissue planes (Fig. 1A). The bones of the arm were intact. The child was treated with antibiotics and compression dressings. Five days after injury, accumulations of fluid and blood beneath the skin caused scalloping of skin contours. Repeat x-ray examination again reveals soft tissue edema and loss of the normal tissue planes (Fig. 1B).

A second patient, also 2½ years of age but relatively tall, also had her hand caught in the power rollers which involved her arm up to the supracondylar region. Her injury was manifest on physical examination by diffuse swelling of the forearm and an abrasion over the dorsum of the supracondylar region. X-rays of the arm showed swelling of the soft tissues and loss of sharpness of the normal soft tissue compartments (Fig. 2). The bones of the limb were not fractured.

DISCUSSION

Power driven wringer washing machines are still being sold today. When a child's fingers and arm are caught in the moving rollers, a typical compression injury of the soft tissues results. The extent of the injury depends on the gap of the rollers, the speed of rotation, the age and height of the child and the length of time the arm is caught within the rollers.

The tissues are compressed through the narrow gap of the rollers tending to abrade and burn, and at the same time slide the soft tissues over the rigid bony structure. When the arm is removed from the rollers, the skin returns to its normal location. The vascular network between the subcutaneous tissue and the underlying fascia is disrupted in proportion to the severity of the injury. Spaces are then formed between the deep fascia muscles and the skin within which edema, fluid and blood accumulate. Necrosis of the skin may occur in

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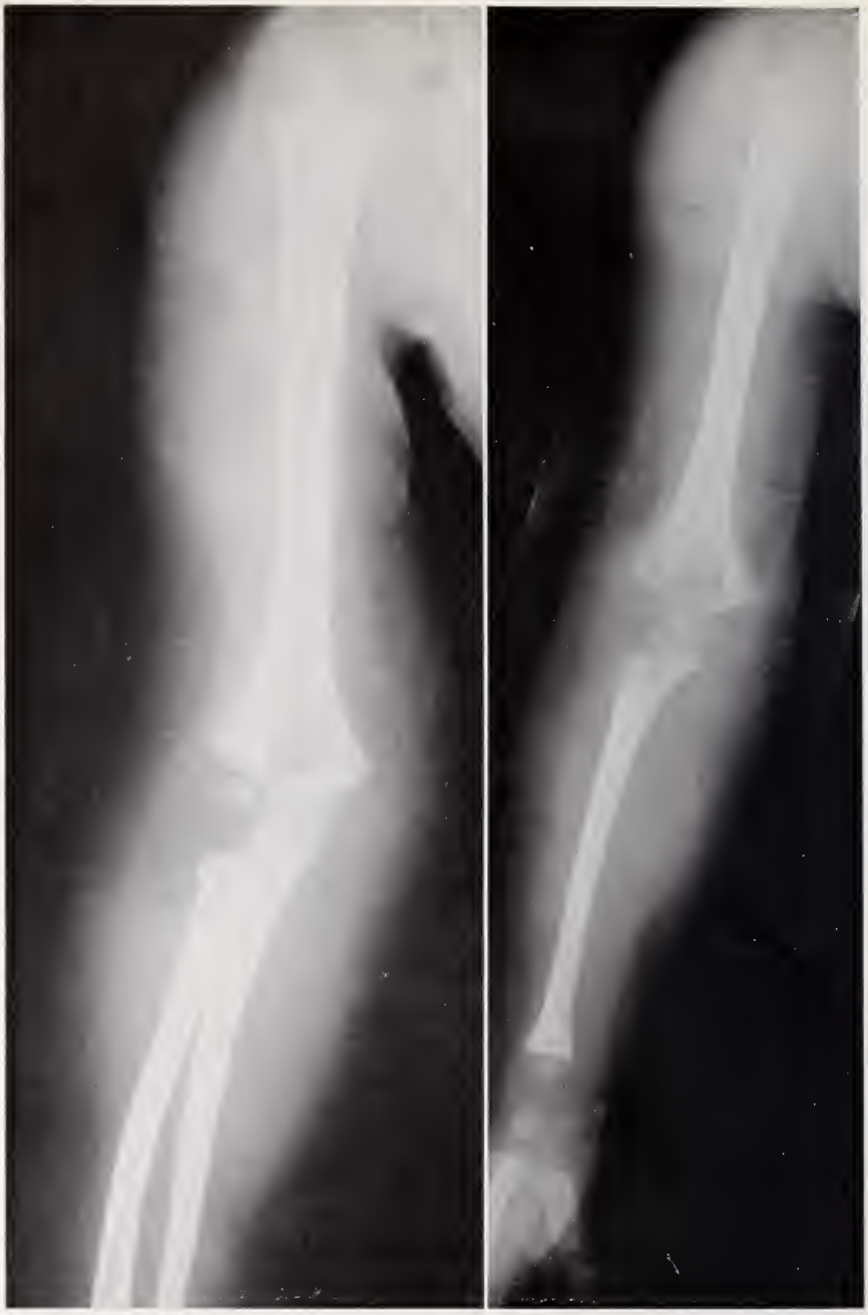
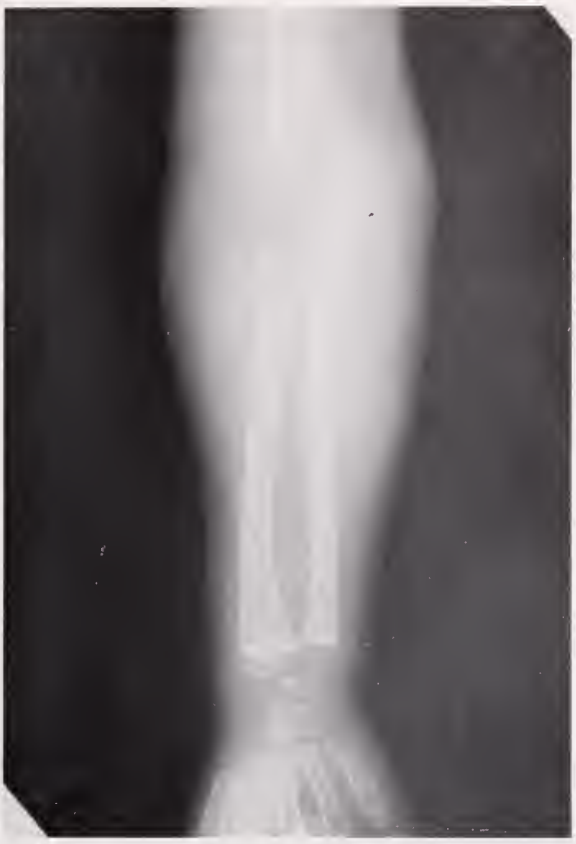


Case 209, Fig. 1A. Soft tissue changes from wrist to axilla showing diffuse swelling and areas of subcutaneous hemorrhage. Marked changes of tissue damage are present in the axilla.

Case 209, Fig. 1B. Re-examination of the same patient 5 days later shows subcutaneous accumulations of blood beneath the skin with scalloping of the skin contours (arrow). The subcutaneous hemorrhage is still very evident.

areas where the vascular supply is most compromised. Fractures of the underlying bones are uncommon.

Roentgenograms of the extremity performed during the acute stage show severe soft tissue damage worse in the axilla or supracondylar area without



Case 209, Fig. 2. The second child's involvement extended only to the supracondylar region. The findings are generalized swelling, subcutaneous hemorrhage and loss of the normal tissue planes similar to the previous case.

bony fracture. X-rays made after several days typically show scalloping of the skin in addition to the damage to the deeper tissues.

Case Report: Wringer injury of the arm in children.

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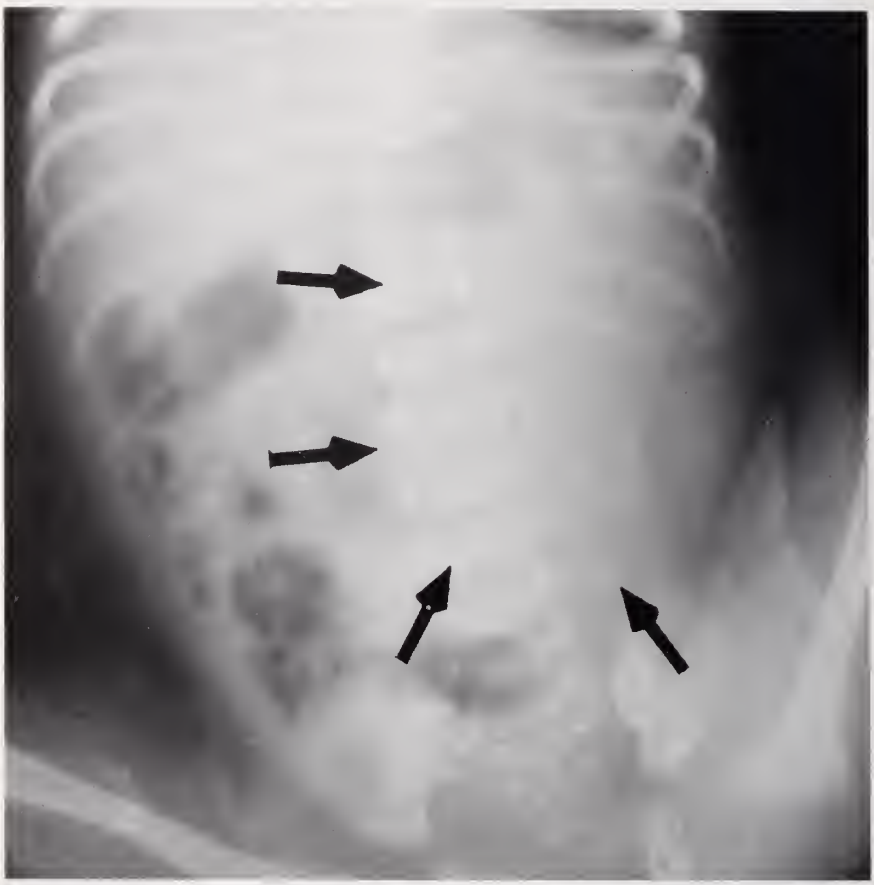
CASE NO. 210

This full term female newborn was the product of a normal pregnancy. Initial physical examination revealed a large, cystic mass within the left side of the abdomen which moved with respiration. X-ray examination of the abdomen performed at that time demonstrated a well-demarcated, round mass within



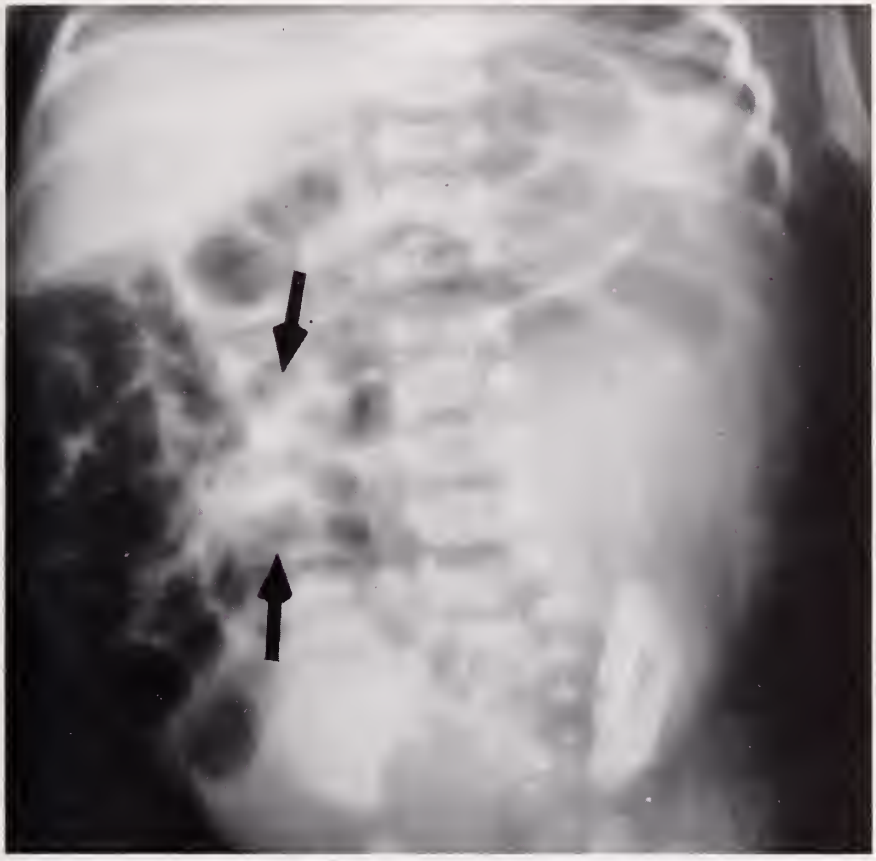
Case 210, Fig. 1. A large mass is present within the left side of the abdomen (along arrows) displacing the gas-filled viscera. No renal shadow can be separated from this.

the left abdomen displacing most of the gas-filled viscera to the right (Fig. 1). An intravenous pyelogram showed no function on the left side (Fig. 2). The right kidney functioned normally. Multicystic kidney was diagnosed and the patient was transferred to The Mount Sinai Hospital where a left nephrectomy was performed. The specimen showed a markedly enlarged multicystic kidney with an atretic ureter.

DISCUSSION

The term multicystic disease of the kidney was established in an effort to distinguish this type of cystic disease from other cystic conditions of the kidney,

for example, polycystic kidneys which are hereditary and ultimately fatal. Unlike polycystic kidneys, which on urography frequently show normal excretion of opaque medium and mild distortion of configuration, multicystic kidneys have no excretion. Anatomically, the involved kidneys are enlarged and irregularly lobulated in contour. Within the parenchyma, there are many cysts of varying sizes held together by loose connective tissue. These cysts may



Case 210, Fig. 2. The intravenous pyelogram reveals a functioning right kidney (between arrows) with no opacification on the left. The left sided mass is again visualized.

communicate with the renal pelvis. In general, the ureter is atretic or absent. Multicystic disease, if bilateral, results in fetal death; if unilateral, the patients survive and the prognosis is good following nephrectomy of the involved kidney.

This disease represents one of the most common renal masses in the neonate and must be distinguished from congenital hydronephrosis. At times these entities can be differentiated by intravenous urography. Cystoscopy to examine the trigone and the ureters is also of importance in evaluating the lesions. An ureteric orifice may well be absent in the multicystic kidney. Other masses

considered in the differential diagnosis are Wilm's tumor and neuroblastoma. Intravenous pyelograms in these conditions demonstrate adequate functioning renal systems with gross distortion and displacement characteristic of either an interrenal or extrarenal mass respectively.

Case Report: Multicystic kidney in a newborn.

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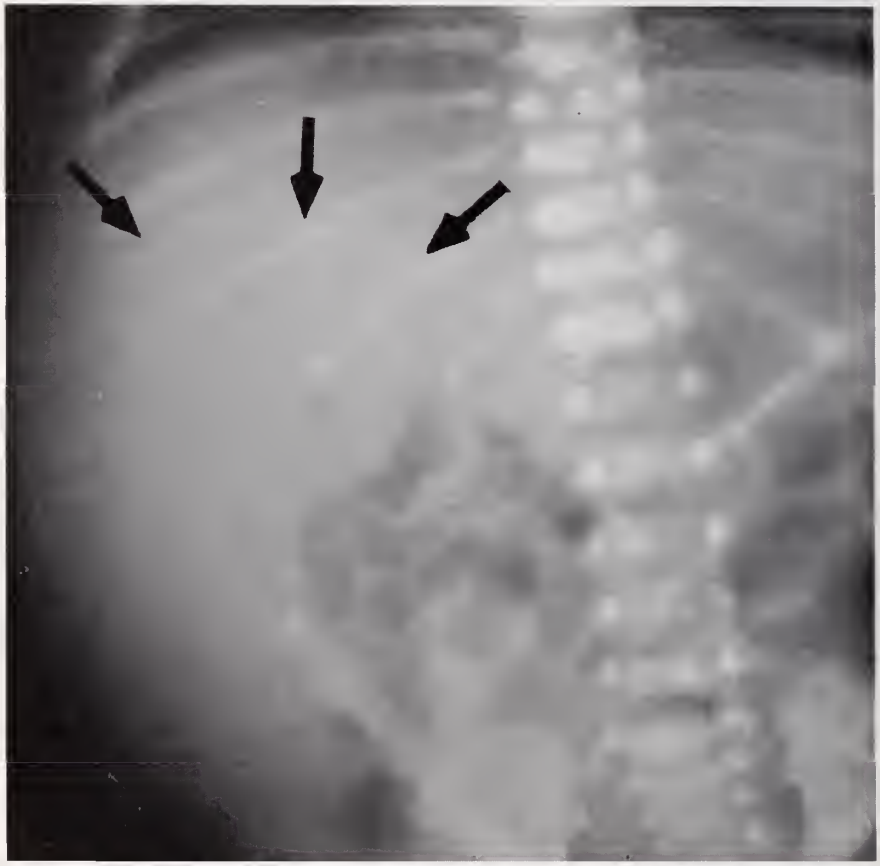
2. Nelson, W. E.: Textbook of Pediatrics, 7th Edition, Saunders, 1959.

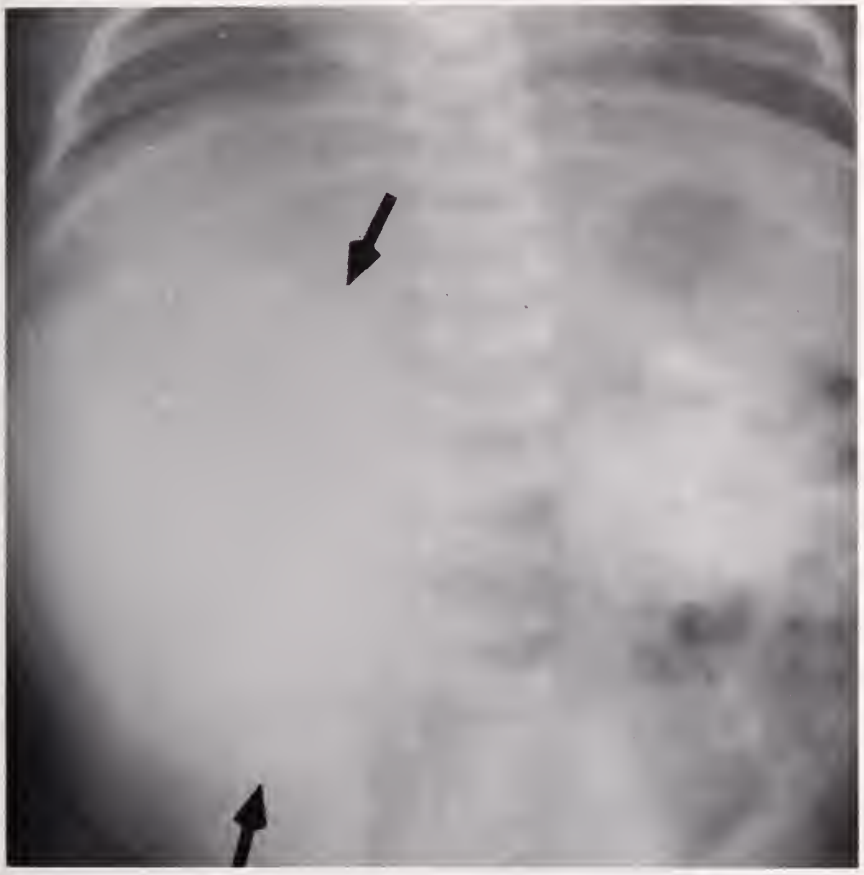
CASE NO. 211

This newborn male infant was the product of a normal gestation. On routine physical examination, the baby was found to have unusual facies, low set ears,



Case 211, 1A. Antero-posterior film during the course of intravenous pyelography reveals a thin rim of opacified renal cortex outlining a large round hydronephrotic sac. This is best seen in its upper half (along arrows). This has been termed the "crescent sign."

hepatosplenomegaly, a large mass in the right side of the abdomen and dysplasia of the hips. On the second day of life, an intravenous urogram was performed. Preliminary film of the abdomen, revealed a large mass occupying the right side of the abdomen extending from the lower margin of the liver to the iliac crest and from the midline medially to the flank laterally. There was bulging of the right side of the abdomen. The gas-filled bowel was displaced to the



Case 211, 1B. Antero-posterior film of the abdomen performed 24 hours later, reveals opaque medium within the hydronephrotic right kidney (between arrows). The left collecting system is moderately dilated.

left. After the intravenous injection of 8 cc of contrast medium, the mass appeared to be lucent when compared to the tissues around it. Two hours later, a thin crescent density was seen outlining the unopacified mass (Fig. 1). X-ray examination performed the following day showed the opaque medium in the dilated hydronephrotic sac of the right kidney (Fig. 2). The left kidney also displayed mild hydronephrosis. A nephrectomy was then performed confirming the presence of a massive hydronephrotic kidney. The site of obstruction was at the uretero-pelvic junction.

DISCUSSION

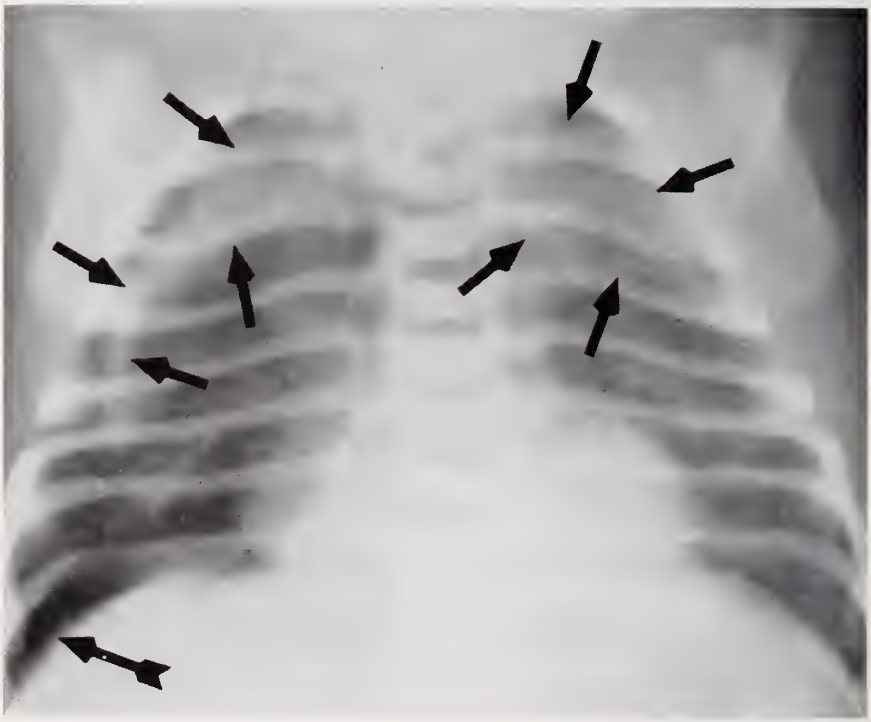
The thin rim of density outlining the hydronephrotic mass seen on intravenous pyelography represents a nephrogram of the remaining cortical tissue of an almost completely obstructed kidney. This has been called the "crescent sign." Allen *et al.* have recently reported four cases of patients with obstructions of the ureteropelvic junction with massive hydronephrosis secondary to this obstruction, where the "crescent sign" was well demonstrated. He and his coworkers feel that the sign is specific of this severe type of hydronephrosis. *Case Report:* Congenital unilateral hydronephrosis in the newborn.

REFERENCE

1. Allen, R. P., Condon, V. R., and Collins, R. E.: Multilocular Cystic Hydronephrosis Secondary to Congenital (Ureteropelvic Junction) Obstruction. An Adjunct to Diagnosis with Intravenous Urography. Radiology, 80: 203, 1963.

CASE NO. 212

One hour after birth, this male infant became cyanotic and dyspneic. X-ray examination of the chest in the frontal and lateral views demonstrated a pneumothorax and a pneumomediastinum (Figs. 1A, 1B). No subcutaneous air



Case 212, Fig. 1A. Anteroposterior view of the chest reveals a sharply delineated crescentic density in the superior mediastinum (along arrows). There is accentuation of the cardiac borders also by mediastinal air. There is a bilateral pneumothorax without mediastinal shift (winged arrow).

collection was noted. The patient was placed in an oxygen tent and his condition remained stable. Four hours later, the patient's condition deteriorated and multiple punctures in the right and left parasternal regions were performed, followed by thoracotomy. The patient's condition continued to deteriorate and he expired a few hours later.

At autopsy, there were bilateral pneumothoraces and a loculated pneumomediastinum of the anterior mediastinum. The loose areolar tissue of the mediastinum was ballooned up into bullae which displaced the thymus anteriorly

Case 212, Fig. 1B. Lateral view of the chest again reveals the thymic shadow outlined by air in the anterior mediastinum (between arrows).

and upwards. Interstitial emphysema was found in the lungs as well as severe bilateral pneumonia. In addition, the baby had severe renal hypoplasia which, in itself, would be inconsistent with survival.

DISCUSSION

The concentric configuration of the thymic lobe extending laterally within the thorax was termed by Moseley (1), as the "thymic spinnaker sail sign." This appearance is diagnostic of loculated emphysema of the anterior mediastinum. Thymic elevation is usually unilateral but, in severe cases, such as in the present patient, it may appear bilaterally. The underlying mechanism causing the pneumomediastinum is increased alveolar pressure with resulting

rupture of the alveolar basement membrane. The alveolar air dissects along the perivascular sheaths to the mediastinum and from there to the pleural cavities and occasionally into the subcutaneous tissues of the neck. If it remains loculated within the anterior mediastinum, the thymus is displaced both superiorly and laterally. Generally, the air is absorbed rapidly. With persistent admission of air into the mediastinum, a tension emphysema can develop. This represents a medical emergency because of the consequent acute circulatory and respiratory embarrassment.

The underlying cause of increased alveolar pressure in this case was attributed to the extensive bilateral pneumonia. Excessive resuscitation at birth or tracheobronchial obstructions are other factors that may lead to alveolar rupture with resulting pneumomediastinum. It is noteworthy that this child had hypoplasia of the kidneys which is frequently associated with hypoplasia of the lungs.

Case Report: Pneumomediastinum in the newborn.

REFERENCES

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2. Jewett, J. C., Adler, R. H., and Takeri, S. A.: Tension Pneumomediastinum in the Newborn. J. Thoracic and Cardiac Surgery, 43: 510, 1962.

CASE NO. 213

This baby girl was noted at birth to have defective clavicles and excessively widened fontanelles. The remaining portion of the examination was within

Case 213, Fig. 1. The central portions of the clavicles are absent (arrows).

normal limits. X-rays of the chest showed aplasia of the middle portions of the clavicles (Fig. 1). The pubic bones were not ossified (Fig. 2). The skull showed poor ossification of bone and widened fontanelles and sutures (Fig. 3). The mother was found to have excessive bossing of the skull as well as abnormal dentition. X-rays demonstrated parietal bossing as well as multiple Wormian bones and defective clavicles (Fig. 4). Radiological examination of the mother's pelvis showed poor ossification and separation of the pubic bones, as well as

Case 213, Fig. 2. There is no ossification of the pubic bones.

Case 213, Fig. 3. The skull shows poor bony development with widened sutures and fontanelles.

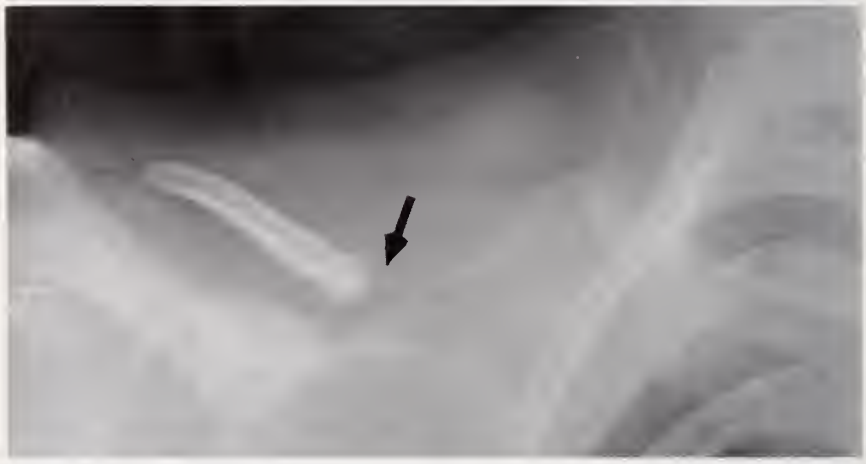
delayed union at the ischiopubic joint (Fig. 5). Another sibling showed no stigmata of the disease.

DISCUSSION

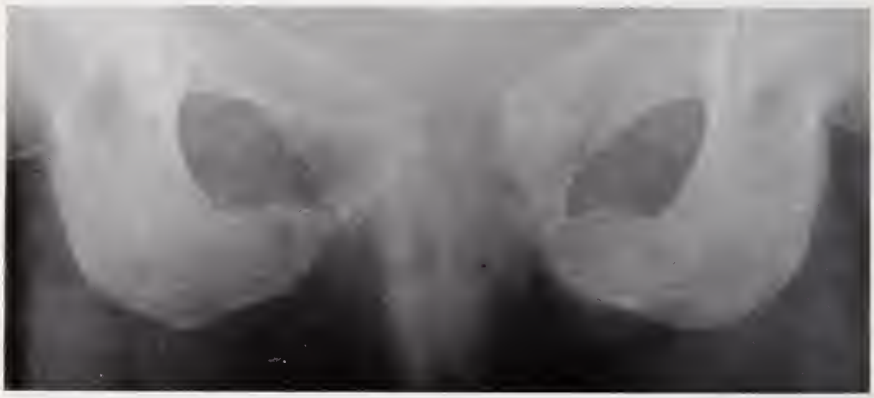
Cleidocranial dysostosis is a familial disease which is transmitted through an autosomal gene. The bony deformities of both mother and child are similar.

Initially, the disease was thought to be related to defective membranous bone formation. However, many changes occur in bones of cartilaginous origin.

Major defects occur in the cranium which show poor ossification of the bones with wide fontanelles and abnormal development of the cranial sutures. Closure of fontanelles is incomplete and open sutures persist into late childhood. Numer-



Case 213, Fig. 4. Here similarly, the central part of the clavicle is absent (arrow).



Case 213, Fig. 5. The pubic bones are poorly developed and there is separation at the symphysis as well as no union at the ischiopubic joint.

ous Wormian bones arise from accessory ossification centers and there is bossing of frontal, parietal or occipital bones. Hypertelorism is frequent. The changes of the clavicle consist of either absence or defective development of one or both bones. The clavicle has three ossification centers, any one or all may be absent. Delayed ossification of the pubic bones and separation of the symphysis are other frequently associated abnormalities (1).

Many other defects are frequently associated with cleidocranial dysostosis,

i.e. incomplete closure of the neural arches, abnormalities of the base of the skull, poor development of facial bones and sinuses, deformity of the phalanges, accessory distal epiphyses of the distal and proximal phalanges and abnormal dentition. Most of the lesions are restricted to the osseous system. Central nervous system defects also have been described (2).

Case Report: Cleidocranial dysostosis in mother and child.

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2. Soule, A. B., Jr.: Mutational Dysostosis. J. Bone and Joint Surgery, 28: 81, 1946.

MONOGRAPHS

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Challenges in the Study of Brain Chemistry

OLIVER H. LOWRY, M.D.

St Louis, Missouri

Let me orient what I have to say around a fact and a conviction. The fact is that the study of the brain is difficult; the conviction is that it is not *too* difficult, that ways can be found to solve the most subtle problems of normal and abnormal brain.

Failure to take this ambivalent attitude toward general problems of nature may be an important reason for the long historical delay in the development and use of scientific research. Many philosophers, through the centuries, did not appreciate the complexity of nature; each tried to solve great problems by himself and consequently neglected to gather small, solid facts on which the next wise man could soundly build. Other great minds of the past thought the world so complicated that it was scarcely worthwhile to try to understand it.

With this lesson from the past in mind, my purpose is first to suggest some of the difficulties in the study of brain chemistry and the chemical changes associated with disease, and then to present evidence that the difficulties are not insurmountable if we are reasonably patient.

There are at least three major problems in studying chemical changes in diseases of brain. In the first place the structural complexity of brain makes gross chemical analyses difficult to interpret. Even a few milligrams of brain contain an almost hopeless mixture of axons, dendrites, myelin, and glial elements. Second, if the architecture of the brain is complicated, the biochemical machinery of any particular cell is even more complex. There must be thousands of different enzymes present, together with their substrates and coenzymes. These function in and around complex structures made of protein and of complicated lipides, and all these compounds are dominated by a complicated hierarchy of nucleic acids. Obviously, trouble shooting when something goes wrong might be pretty difficult, particularly since the chances are that the chemical substance at fault would be an unknown one. May I digress to point out that neurochemistry is merely biochemistry and that neurochemistry advances as biochemistry as a whole advances. A discovery made in bacteria or in grasshoppers or in liver or skin, is a discovery in brain. Neurochemists working alone would be a long time on the road.

In addition to the structural and chemical complexity of brain, there is another difficulty in the chemical study of brain disease. The secondary reactions of brain to damage produce changes which would be reflected in any chemical analysis

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and thereby confuse interpretation. The microscopist can see around the macrophage or the dead neuron and examine whatever he may be most interested in. He can focus on viable tumor cells and ignore, if he wishes, all other things that may be mixed with the intact cells. The chemist on the other hand scoops everything together into his test tube. He must learn to make allowance somehow for the complicating constituents. Here, more experimental studies would be very helpful. It is necessary to know more about the chemical events in Wallerian degeneration, in chromatolysis, after different degrees of ischemia, and so on. A background from experimental studies would greatly aid interpretation of results in disease.

Some of these difficulties in the chemical study of brain disease could be circumvented by carrying out microchemical analyses of individual histological elements. Let me, therefore, describe some of the tricks which make it possible to perform such analyses.

There are four overall requirements that must be met if we are to have meaningful quantitative histochemical analyses. First, the histological sample has to be isolated with minimal change in the constituent to be measured. Next, the size of the sample needs to be determined. Third, analytical methods of sufficient sensitivity are required. Finally, something worth measuring must be determined. The last may be the hardest. Although most cell constituents might be worth measuring if we understood their full significance, at a given stage of our ignorance the concentrations of certain substances may convey little meaning. For example, the amounts of alkaline phosphatase in various neurons seem at present less meaningful than the concentrations of lactic dehydrogenase, but neither one may be very relevant for the study of brain disease.

In our scheme of histochemical analysis, the tissue is frozen in Freon chilled to its freezing point, −150° (1). The quick freezing is to keep ice crystals as small as possible. Sections are cut at −15° to −25° in a constant temperature box, and the sections are placed in the holes of a rack which consists of a 4 mm thick aluminum block drilled with eight or ten holes and sandwiched between two microscope slides (Fig. 1). Four of these racks are placed in a large glass tube provided with a ground glass cap and stopcock in which the samples are easily dried at −40° under vacuum.

From the initial freezing until the samples are thoroughly dry, great care is taken to keep the tissue below −10°, but thereafter the samples can be brought to room temperature and dissected at leisure. Tests have shown that nearly all enzymes which tolerate freeze-drying in the first place (*i.e.* most enzymes) will also tolerate, without loss of activity, several hours at room temperature and years at −20°. Sections cut at 20 μ are useful for many purposes, but sections as thin as 5 μ are needed for certain purposes, for example, studies of retinal layers.

Dissection is carried out with knife blades which are splinters of razor blades 0.5 to 1 mm along the sharp edge and 2 or 3 mm long. These are sealed with a strong cement to a short piece of copper wire in a wooden handle (Fig. 2). The wire permits easy adjustment of cutting angle. If a very short piece of horse hair or synthetic bristle is interposed between blade and wire the resulting flexibility

makes the knife easier to use. The somewhat delicate tissue is held down for dissection with a biologist's hair loop. There is no great difficulty in dissecting free hand to within 10 μ of a desired point or line, or by using one end of the knife blade as a rest point and fulcrum, even sharper free hand dissection is possible. Alternatively, a micromanipulator may be used. A "hair point," which is simply a hair with a fine point on the end of a suitable handle (Fig. 2), is convenient for transferring the dissected samples.

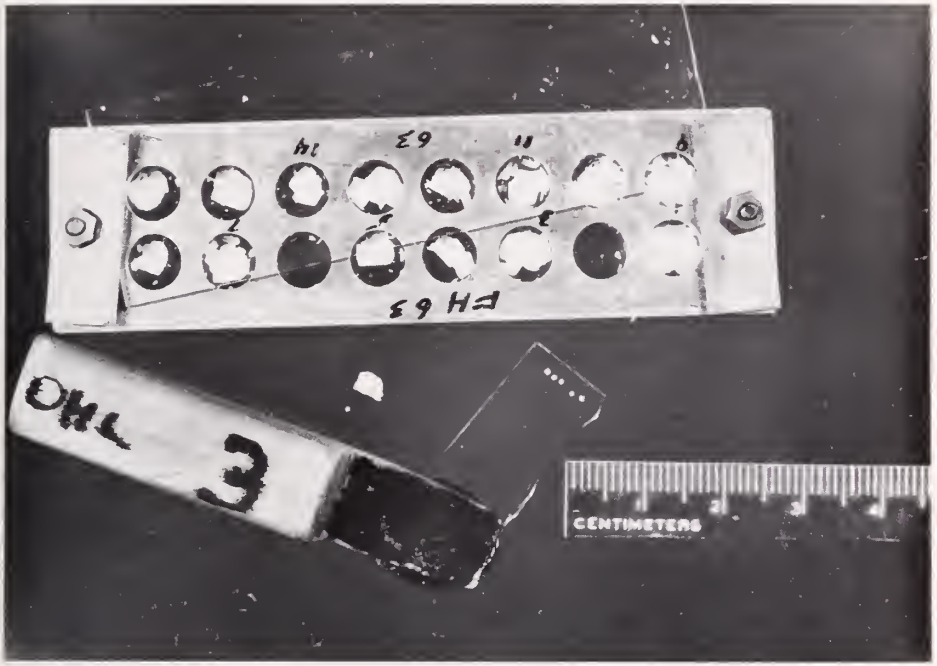


FIG. 1. Aluminum block with glass cover and bottom for receiving, drying, and storing frozen sections. The top glass slide is partly removed and most of the holes contain sections, which have already been dried at −40°. Also shown is holder made of wood and glass for transporting samples of the dissection. Five dissected samples, weighing about one μg each are shown on the holder.

Although the frozen-dried tissue has been neither fixed nor stained, many structures are clearly visible (Fig. 3).

After dissection, weighing seems to be the simplest means for measuring sample size. The balances used are merely fish poles made out of fine quartz hairs (Fig. 4). The sample is placed on the balance tip with a hair point and the displacement is measured with a micrometer ocular in the eyepiece of the same low-power, wide-angle microscope used to supervise the loading. The balance shown is suitable for samples weighing 0.2 to 1 μg. Much more sensitive balances are available. The most sensitive to date, is only 5 mm long, the fiber 0.3 μ in diameter, the load limit 0.001 μg and the sensitivity 2×10^{-6} μg (2 picograms) or about seven per cent of the dry weight of a red blood cell.

After weighing, the remaining step is the chemical analysis itself. The sensitivity requirements vary enormously with the structure to be analyzed and the substance to be determined. The upper limit of useful sample size might be taken as about one μg. The reason for picking this figure is that it is seldom possible to obtain samples weighing much more than this which are appreciably simpler than whole brain. At the other extreme, the smallest nerve cell body has a dry mass of about 0.000,05 μg. There is present in one μg of average dry brain enough of one of the more abundant enzymes, lactic dehydrogenase for example, to convert about 10^{-7} moles of substrate to product in an hour's time. There are,

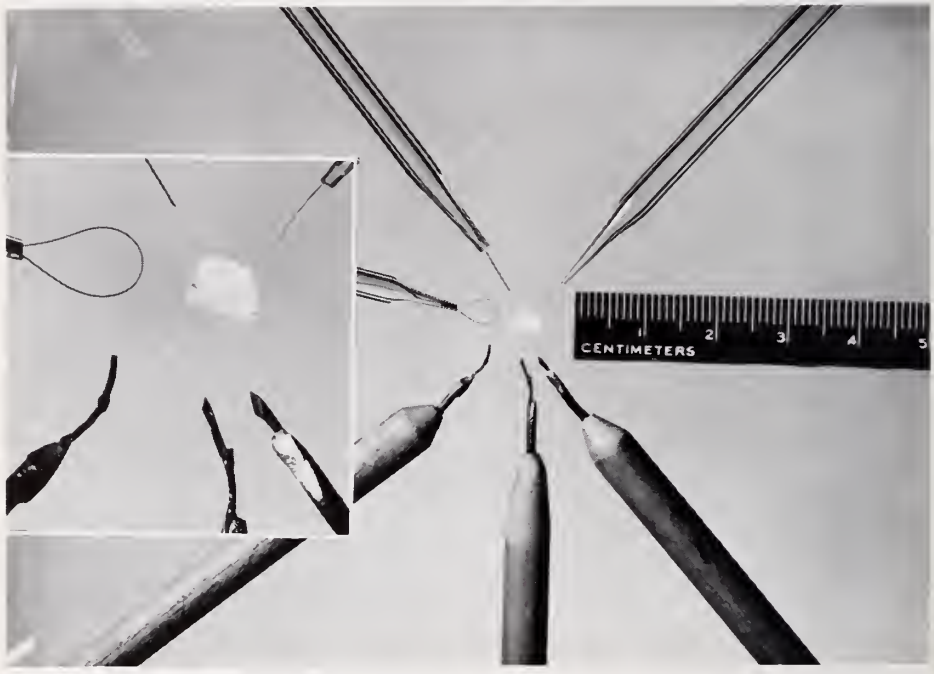
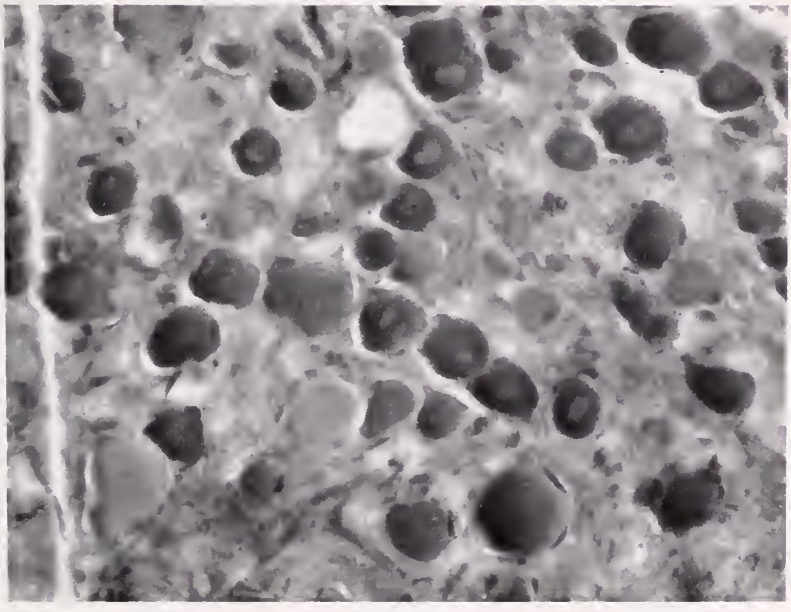


FIG. 2. Tools used for dissecting frozen-dried sections. Shown are two knives, a hair loop and a coarse and fine hair point (see text).

however, important enzymes which are 10,000 times less active than this. The tissue concentrations of the *substrates* of the various enzymes are much lower than the amounts of product that the same enzymes can produce in a reasonable period. For example, there are only about 10^{-11} moles of lactate in one μg of average brain, whereas there may be no more than a thousandth as much of other important substrates. This means that the smallest nerve cell body may contain as little as 10^{-19} moles of one of the less abundant substrates. Thus there is an enormous range in the sensitivity that would be required for one or another histochemical problem.

To achieve the necessary sensitivity there are many general analytical possibilities, of which colorimetry, fluorometry, and gasometry are the most widely

A



B

FIG. 3. Frozen-dried cerebellum, 3A, and dorsal root ganglion, 3B, as they appear during dissection. The cerebellum is 20 μ thick and the ganglion 10 μ. There has been no fixation, staining or embedding.

used. Of these, fluorometry has many advantages. All things being equal, it is at least a thousand times more sensitive than colorimetry.

For this reason, a general analytical system has been worked out based on the fluorescent properties of the pyridine nucleotides, DPN and TPN. The system capitalizes on the fact that almost every constituent of the cell can be measured directly or indirectly with a pyridine nucleotide system. The following can serve to illustrate the system:

$$\text{Alanine} + \alpha\text{-ketoglutarate} \xrightarrow[\text{aminase}]{\text{trans}} \text{pyruvate} + \text{glutamate} \qquad (1)$$

The pyruvate produced is a measure of either alanine, α-ketoglutarate or the transaminase, depending on which component is omitted. The pyruvate produced is in turn measured by a second reaction.

$$\text{Pyruvate} + \text{DPNH} \xrightarrow[\text{dehydrogenase}]{\text{lactate}} \text{lactate} + \text{DPN}^+ \qquad (2)$$

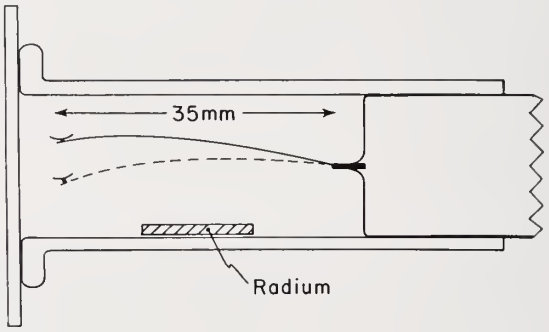


Fig. 4. Fishpole balance. The balance shown has a sensitivity of 0.002 μg and a load limit of one μg; which corresponds to a displacement of 2.5 mm at the tip. The quartz fiber is about 10 μ in diameter.

The second reaction is stopped by adding acid, which destroys excess DPNH but does not affect the DPN^+. To the sample is now added strong alkali which converts DPN^+ to a very fluorescent compound, as discovered by Kaplan *et al.* (2). As little as 10^{-11} moles of DPN^+ can be measured in one ml.

If this sensitivity is not sufficient, the DPN^+ can be measured by allowing it to catalyze a two enzyme cyclic process, which in effect amplifies the DPN many thousand fold. The reagent for this purpose contains lactic dehydrogenase, glutamic dehydrogenase, lactate, α-ketoglutarate and ammonia. The DPN^+ added starts the cyclic process represented by the following two sequential reactions:

$$DPN^+ + \text{lactate} \xrightarrow[\text{dehydrogenase}]{\text{lactate}} \text{pyruvate} + \text{DPNH} \qquad (3)$$

$$DPN^+ + \text{glutamate} \xleftarrow[\text{dehydrogenase}]{\text{glutamate}} \alpha\text{-ketoglutarate} + NH_4^+ + \text{DPNH} \qquad (4)$$

Because the enzymes are present at high levels, the DPN^+ is quickly reduced to DPNH by reaction 3 and then quickly oxidized back to DPN^+ by reaction 4.

Each time a molecule of DPN goes around the cycle a molecule of pyruvate and a molecule of glutamate are produced. With the low levels of DPN used, the yield of these products in a fixed time interval is proportional to the DPN concentration. It is easy to achieve a 5000-fold yield in an hour. Therefore, if there are, for example, 10^{-14} moles of DPN present, 5×10^{-11} moles of pyruvate can be produced in an hour. At this time the mixture is heated to destroy the enzymes, and the pyruvate is measured as described above (reaction 2, followed by acid and then alkaline treatment).

Since one of the products of reaction 2 is again DPN^+, the overall result is to

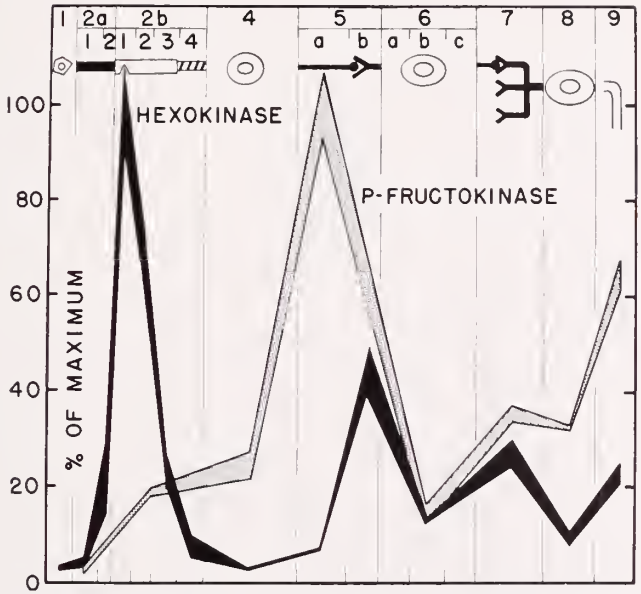


Fig. 5. Distribution of hexokinase and phosphofructokinase in monkey retina. The line widths at the center of each layer equal two standard deviations for that layer. The points have been connected for better visualization, but this does not imply a gradual transition of values from one layer to the next. The layer widths are drawn roughly proportional to actual layer thicknesses. The peak values for hexokinase and phosphofructokinase were, respectively, 27 and 32 moles per kg of fat-free dry weight per hour. (Reprinted from Lowry *et al.* (4).)

produce 5000 moles of DPN^+ for every mole of DPN^+ present before cycling. Therefore, if still more sensitivity is required, the DPN^+ can be amplified another 5000 fold in a second cycle for an overall gain of 25,000,000. This provides sufficient sensitivity in principle to measure 5×10^{-19} moles of original substrate in a final volume of one ml. Contrary to expectation, in spite of the greatly increased sensitivity resulting from cycling or recycling, there is not necessarily any decrease in analytical precision (3).

With the tools described, data have been obtained which show that the central nervous system is fully as heterogeneous as had been anticipated. In the retina, for example, there are found to be dramatic differences in the distribution of enzymes even within different parts of the same cells (Fig. 5). In the first retinal

neuron (rod and cone cells), hexokinase is almost entirely confined to the outer portion of the inner rod and cone segments, whereas all the other members of the glycolytic cycle so far measured are much richer at the distal end of the cell (4). Presumably glucose enters the avascular outer retinal layers from the choroidal blood vessels, becomes phosphorylated in the inner segments, and then diffuses along the neuron as glucose-6-P or fructose-6-P to the other end.

Although one might have expected various central tracts to be much alike in composition, rather large differences have been found among them (Fig. 6). Glucose-6-P dehydrogenase, for example, may be three or four times richer in heavily myelinated tracts than in those that are lightly myelinated, whereas the reverse is true for glutamic aspartic transaminase.

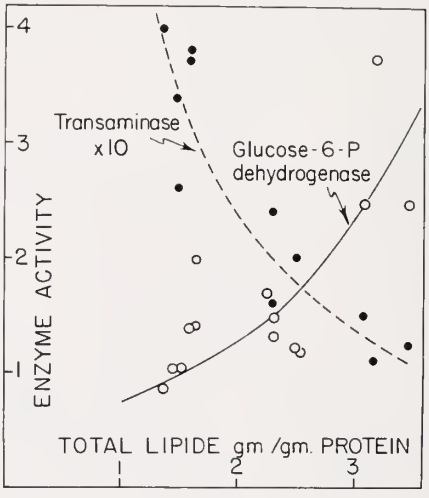


FIG. 6. Glucose-6-P dehydrogenase and glutamic-aspartic transaminase in a variety of central tracts in rabbit. (Adapted from McDougal *et al.* (5, 6).)

Other illustrations of heterogenicity are provided by the data of Hirsch and Robins who found that dorsal root ganglion cell bodies are three fold richer than anterior horn cell bodies in β-galactosidase, and that both are many times richer than neuropil near the anterior horn cells (7).

Studies of diseased or damaged nervous tissue with quantitative histochemical methods are fragmentary so far, but the results of Robins and co-workers demonstrate some of the possibilities. After sciatic section (8), many enzymes in the affected anterior horn cells are changed very little, but glucose-6-P dehydrogenase increases over a 35 day period to three times the normal level. McCaman and Robins made an extensive study of Wallerian degeneration in optic tract and tibial nerve and found that although in general the changes in lipids and enzymes were comparable, the time course was many times longer in the central tract (9, 10). In the case of a few enzymes, there were also large quantitative differences between the behavior in central tract and peripheral nerve.

These illustrations are taken from experimental material; it is more difficult to study natural diseases of unknown origin. The following is a speculation as to the possible way that chemical analyses might be helpful in studying disease processes.

In the first place, gross chemical analyses and quantitative histochemical analyses can complement each other. If the composition of the component parts of brain is known, the analyses of a gross sample of brain can tell something about the abundance of those parts in the sample. To give a perhaps trivial example, since most cells have the same constant amount of DNA, measurement of DNA in a 10 mg brain biopsy specimen would indicate the number of cell bodies present and might be a valuable supplement to microscopic cell counts. Similarly, the amount of sphingomyelin present can be used to assess the degree of myelination or the proportion of myelinated fibers in a damaged tract. The more that is known about the composition of normal histological structures, the easier it becomes to interpret the composition of a gross specimen.

The study of genetic diseases of the CNS is simplified by the fact that a specific metabolic defect is likely to affect many kinds of cells throughout the body. So far, success in the study of genetic diseases affecting the central nervous system has been limited to those in which the disorder is also manifested outside the brain, and the clues have come from chemical study of urine or blood rather than brain. It seems probable that the causes of some of the other diseases of the nervous system will be discovered in the same way by studies of non-nervous tissues or fluids, rather than by analysis of the brain itself.

In other cases, however, the changes outside the brain may be so meagre as to escape detection. In this situation what can be done? As indicated above, much time has been spent measuring enzymes in various structural components of the normal CNS. The question is, how useful would it be to measure the amounts of this or that enzyme in the histological structures of diseased brain? There are thousands of enzymes. If only one of these were missing it might be a long time before someone happened to measure it. More hopeful, I believe, would be to measure the substrates of some of these enzymes. One missing or inhibited enzyme can cause changes in the levels of many substrates both upstream and downstream from the block.

Also it should not be necessary to limit oneself to microchemical studies of individual nervous elements. It might be easier to study larger tissue samples. If changes were found, one could then proceed to examine individual histological components. This approach should suffice unless the cells affected are so few and far between as to be without quantitative influence on the gross analyses. This approach might also fail if there should be a significant degree of cellular infiltration or necrosis.

In summary, it seems to me reasonable to take the following position:

Brain chemistry offers many interesting difficulties. Some of these difficulties can be circumvented through direct microchemical analysis along the lines indicated. In the case of normal brain, the measurement of both enzymes and their substrates, (at the cellular and subcellular level) can tell a great deal about how brain machinery operates.

In the case of brain disease, it may be more efficient to study the substrates first. Furthermore, with histochemical information about the normal available as a guide, it may be possible to learn much from gross chemical studies of diseased brain, particularly if one is aware of the chemical consequences of secondary necrosis or degeneration.

It may take a long while and a lot of work to understand our master tissue in health and disease, but it is surely worth the effort.

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Experiences in Teaching Basic Psychiatry to Medical Practitioners at The Mount Sinai Hospital, New York

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Demands for postgraduate psychiatric training have resulted in a sharp increase in courses and seminars for nonpsychiatrist physicians in recent years. Sheeley, in a survey published in January, 1962, found that of 53 postgraduate courses for instruction in psychiatry and psychosomatic medicine, 40 had been started during the past two years alone (1).

The pioneering Minnesota experiment in teaching psychotherapeutic medicine to physicians, which took place in 1946, was successful for a variety of factors; first, the methodological approach which combined education with training (2). The physicians taking this course received theoretical instruction in addition to a body of clinical information, and at the same time they were also *trained* in the very techniques that their instructors had been talking about in their orientation lectures. If several attempts during the following years to achieve substantial results with series of lectures and seminars at Mount Sinai and other institutions failed, it was in part due to the fact that such training and the rather specialized techniques of interviewing were absent from the curriculum.

One such course at The Mount Sinai Hospital extended over twenty weeks, taking place once a week for half a day and consisting of lectures, alternating with discussions of case histories and of clinical problems which the students encountered in their practices. A number of seminars followed in successive years in which the medical practitioners were offered what seemed to be abstract conceptualizations which they were expected to apply to their daily practice. These courses were not very successful, from our point of view, since they did not result in any change in the basic practice of the physician.

In a report formulated by the Committee on Therapy of the Group for the Advancement of Psychiatry, it was pointed out that "Specific techniques must be acquired in actual clinical situations, preferably under expert supervision, in which many adverse clinical problems are encountered." Some of the other important variables which act as coefficients in a course of this kind are the personalities and teaching skills of the instructors, the clinical material used for didactic purposes, even the setting in which the instruction takes place, and the student-teacher relationships. *Expectation* is an important factor in itself. This goes for both the student and the teacher. Inner resistances on the part of the teacher and profound skepticism about the value and result of such an

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undertaking will communicate themselves subtly and insidiously to the student body. In our experience, we found that excessive skepticism and very low expectation on the part of the student as to the benefit of such instruction customarily leads to the phenomenon of the problem student who tries to involve his instructors in lengthy polemics and quarrelsome arguments. He is not really open to accept new ideas or to learn new techniques.

Before embarking on a critical examination of the structure and curriculum of a teaching program of this nature and the reactions of the student-physician, we should first scrutinize the philosophy which gives direction and a specific frame of reference to its teachers.

It has been said that the seasoned medical practitioner—in contrast to the medical student—needs only a few comprehensive lectures on the various aspects of psychosomatic problems or other topics involving emotional problems followed by "free discussion," and that anywhere from six to twelve such seminars held "in the relaxed atmosphere of mature doctors" will be sufficient to provide the sought-for knowledge and know-how. But is it really primarily a question of acquisition of new knowledge, or is it not instead to a very high degree a question of gaining a new point of view, of learning to think along new avenues, and of acquiring a limited, though not inconsiderable, change of attitude and outlook toward the doctor-patient relationship (to paraphrase a comment made by Balint) (3)? With this in mind, we set up a course of instruction in psychiatry for medical practitioners at The Mount Sinai Hospital, which emphasizes clinical work in supervised sessions with suitable patients from different departments of the general hospital. We felt that mere lectures and seminars do not contribute enough to fill the basic needs of the practitioner to enable him to arrive at a significant change in inner attitude. We were reminded of Osler's warning that senior medical students and young doctors are "too often given the stones of the lecture room for the bread of the wards" (4). Quite recently this instructiveness of "practical teaching" was highlighted by an editorial in the Archives of General Psychiatry in which a practitioner (M. C. Greengold) said: "A round of the currently available postgraduate education in psychiatry is as edifying as a preface, followed by a publisher's note, followed by an introduction, followed by a foreword, concluding with a summary of the above. Deletion, as well as addition, would certainly enhance the book. May we ask our lecturers to dispense with the information that — per cent of our patients really have emotional problems?... Please do not explain how much good just listening does for our patients" (5).

The course extends over a period of nine months. It is given by a teaching staff consisting of three psychiatrists, a psychologist, a social worker, a program coordinator and supervisor of the technical staff. It takes place two mornings each week, on Wednesday and Saturday, from 9:00 a.m. to 1:00 p.m. A minimum of six, but not more than eight physicians, are selected out of the total group of applicants, usually from 25 to 35 or more, through screening interviews. Doctors who intend to take this course in lieu of a psychiatric residency or those who intend it to be a bridge from their specialty into psychiatry, are not ac-

cepted. This brief screening process revealed that written comments about motivations for seeking such psychiatric instruction relatively late in a doctor's career, usually contain all the proper, conventional reasons, while personal interviews with some of the applicants brought out a variety of undesirable motivations from our point of view. A few applicants wanted psychiatry to stir up sufficient interest in them before taking the plunge into a psychiatric residency. Others saw the course as leading to a safe little position of some kind, based on an expected "certificate" at the end. We had to disappoint all such applicants.

In planning this course we were thinking of the physician who had become aware of changing concepts with respect to psychiatry and the field of general practice and who was seeking the personal experience of applying, under close supervision in clinical work, such concepts as part of the basic psychiatric instruction. We had in mind physicians whose personalities had remained flexible enough to assimilate a new approach to their patients and who were sufficiently motivated by curiosity about the workings of the human psyche to look for a better understanding and new insights into the intricate mechanisms of the mind.

The distribution of specialties among physicians who have participated in this project since its inception in 1959 was as follows:

General practitioners	10
General practitioners with predominantly pediatric practice	2
General practitioner with emphasis on internal medicine	1
Pediatricians	3
Obstetricians and Gynecologists	4
Radiotherapist	1
Internist	1
Anesthesiologist	1
Dermatologist	1
Endocrinologist	1
Public School Physician	1
College Physician (combined with general practice)	1
Oral Surgeon	1
Total	28

The age of the doctors ranged from 35 to 58 years.

The first three mornings are devoted to orientation lectures which deal with:

1. The doctor-patient relationship;
2. History-taking;
3. Initial interview techniques;
4. The all-important issue of alerting the doctor to relevant cues among the data picked up while taking a history, and from general observation of the patient.

These orientation lectures are immediately followed by initial interview technique practice sessions. For these didactic sessions non-psychiatric patients, selected at random from the various medical and surgical departments of the hospital are brought in. The physician-student is made to see that a great deal

of relevant information can be obtained in a well-structured interview which may not take more than 20 to 25 minutes.

The eight weekly hours are divided into three 45 minute interviews with clinic patients, one 45 minute session devoted to individual supervision, and another such period for dictation of clinical notes. This work is followed by one and one-half hours of case presentations and discussions by the entire group with the participation of the social worker and the psychologist. Another such period is at first taken up by group discussions of initial interview technique, which is practiced intensively during the first four months of the course. Thus each doctor shares in the clinical experience of the others. By the end of this phase of the course a total of 35 to 40 initial interviews have been fully discussed by the group. Later on, this period is devoted to a number of formal lectures by liaison psychiatrists attached to various departments at The Mount Sinai Hospital, who relate their observations and experiences in such work side-by-side with medical practitioners in different fields. These lectures and discussions alternate with presentations of the fundamentals of psychodynamics, illustrated by the clinical case material at hand.

The social worker assigned to this project introduces the medical practitioners to the realm of social forces which may affect the patient's life and the social factors which may aggravate illness and interfere with medical care. The collaborative processes inherent in comprehensive treatment are emphasized. Through frequent individual and group discussions of specific case material, the practitioner is made to see that simply "telling the family what to do" is not the answer. He is helped to an understanding of the full impact on the family and on the community of the patient and his problems. It is stressed whenever indicated that the patient's problems reflect family pathology and therefore must be seen in this light if the patient is to be helped. The case worker demonstrates with individual cases that the patient's right to service also belongs to the family and that frequently both patient and family require preparation before they can utilize treatment fully. These sessions with the social worker are, as one student put it, "a real eye-opener." Few doctors have a clear picture of the role of social service in a hospital or agency setting and of available community facilities.

Several conferences were set aside for formal presentations by the psychologist of the workings of the Rorschach, the TAT and other tests for the purpose of at least giving the practitioner an introduction to the understanding of the meaning and usefulness of psychological test results.

The students are assigned three patients each for supportive psychotherapy, under the continued guidance of the teaching staff. Unlike the patients seen in the didactic initial interviews, these patients are carefully screened by the staff. The first of these patients is assigned immediately after the orientation lectures. Two weeks later a second patient is introduced, and at the beginning of the second month, a third patient is added.

Close contact with each member of the group throughout the year in individual supervisory sessions, as well as in conferences and group discussions, enabled

us to observe their reactions to the various aspects of the course in detail. We were thus able to study by practical experiment a number of questions which had been in our minds during the planning stage of this project: Was the course as we originally set it up really going to meet the needs of the practicing physician? Did he come equipped with more or less knowledge and awareness than we assumed? Did he require more theoretical information than we were offering? Were more formal lectures followed by discussions pertaining to psychosomatic medicine indicated? Was our emphasis on clinical experience justified?

The difficulties faced by some of our students became quite apparent at the end of the first month of the course. Instructions on how to take a well-rounded and complete life history had been followed faithfully but the real problem proved to be how to use this material. Some of the students were actually hiding behind an impressive amount of historical data while shying away from any attempt to understand what the patient was trying to communicate to them. The practitioner's discomfort in the presence of an emotionally troubled patient and his inability to link up the material gathered from the patient with a store of knowledge and pertinent experience, which might guide him in evaluating these data, led to evasive maneuvers. A typical example is the physician who tries to enmesh the instructor in differential diagnostic arguments about the "organic" nature of the patient's complaints. He sheds doubt on the reliability of the findings of a medical, hematological or neurological examination reported in the chart. He tries to spend entire sessions pointing out what laboratory tests have not been done and why he would do further exploration along these lines. He has remained preoccupied with the organic aspect of the patient's psychosomatic illness, and he reveals at the same time a deeply ingrained conviction that organic illness precludes emotional conflict. His medical thinking is dominated by a rigid "either/or" attitude: anything due to emotional disturbance is "functional" and therefore cannot be demonstrated until all possible organic causes have been excluded. He may be so preoccupied with hunting for organic clues and so tormented by inner doubts about the usefulness of a psychological exploration, that he remains deaf to the symbolic expressions of his patient's emotional conflicts.

A case in point is the reaction of one of our students to the initial interview of a 43 year old woman who was referred by our liaison psychiatrist attached to the Neurology Service. The patient came to the interview accompanied by her husband. As they entered the office, he tried to direct his wife who walked with great difficulty, supported by a cane, to the nearest chair. She turned to her husband sharply, hissing angrily, "I know where to sit down," and actually pushed him away with her elbow. As soon as she was seated, her facial expression changed to one of great amiability, and she began to talk volubly about her difficulties with her gait, saying that her husband must take her for a fool, because of his repeated warnings when she is about to cross a street, to use first one foot and then the other "as if there was any other way." She went on to describe with apparent satisfaction her husband's limitations both in intellect and intuition. She said that she liked to be in charge at home and direct

things and that certain decisions could not be left to her husband. When asked about any evidence of visual disturbances in the past, she replied that she never had any in her life. (A look at her chart revealed that she had had an optic neuritis with transient blindness sometime ago.) Instead, she talked about "the funny coincidence" of being afraid as an adolescent of losing the use of her legs and eyes, "and that is just what happened to me."

As the patient was about to leave the office, the doctor quickly arose from his chair intent on helping her. The instructor restrained him and motioned him back to his seat. Alone with his instructor the physician opened the hospital chart and pointed to the diagnosis arrived at in the Department of Neurology, "demyelinating disease, probably multiple sclerosis." He was astonished at the instructor's apparent unwillingness to assist this patient who was severely ataxic. He had overlooked the patient's emotional need to demonstrate self-sufficiency in the face of very real obstacles. He had not picked up her repeated hints for her need for a different kind of help. Her remarks that her husband was lacking in understanding and sensitivity had no particular significance for him, while actually this was precisely what the patient wanted—a more subtle understanding of her need to fight off the dreaded helplessness and dependency on husband and daughter. What she most looked for in her present predicament was approval and encouragement, as well as guidance in her difficulties, all of which could be handled by a perceptive physician, perhaps in cooperation with a case worker.

Characteristically, this practitioner tried to turn away from a discussion of the psychological aspects of this case bringing up instead the question of differential diagnosis. A perusal of the chart had not revealed to him the findings of a complete hematological work-up and he insisted that a complete blood count ought to be done in order to eliminate the possibility of degenerative neurological sequelae due to pernicious anemia. He seemed acutely uncomfortable when confronted once more with this patient's family and personality problems, and he finally expressed his impatience with these aspects of the case by saying that he saw no point in helping the patient in her struggle for emotional survival and in her attempts to rehabilitate at work since she was "doomed" anyway. He felt that these efforts should be replaced by a continued search "for any possible organic clue."

It was pointed out that the request for a complete blood count would be made after a recheck with the Departments of Neurology and Medicine, but that in all probability nothing new would turn up in the laboratory and that as he knew, multiple sclerosis was a progressive degenerative disease, which would take its course. Through the mechanism of denial, the true nature of her illness, which this patient described as "my neurotic illness," remained hidden from consciousness despite the progressive impairment of her gait and despite the frightening experience of temporary blindness. The latter was not recalled by her at all. It was emphasized that this was all the more remarkable in a woman of her intelligence and education, who had worked in the television industry where for many years considerable efforts have been made to raise funds for

research in multiple sclerosis. These programs always contain descriptions of the symptoms from which the patient was suffering. The doctor was told that her ego used the denial and the euphoric mood as protective shields against the crushing impact of the truth. It was discussed with him that any attempt to remove the denial and to make her face the facts of her illness would have disastrous results and push her into a deep depression with possible self-destructive acts. Such a danger seemed to have existed a few months prior to the interview, when this patient was severely depressed.

The doctor wanted to do more, such as to prepare the patient for the inevitable. To permit the patient to cling to her defenses as a protection against the unacceptable truth did not seem "scientific," and therefore not satisfactory to him. He continued to be more concerned with the issue of performing the miracle of saving this patient from physical destruction than with the issue at hand: her emotional survival.

Later that morning this interview and the ensuing discussion were brought up in the group conference. The group discussion revealed how difficult it is for many doctors to take the lead from the patient and become attuned to the patient's allusions which signal the proper course to follow in each instance. Again, some of the doctors were looking for a formula, a fixed approach to all patients with a terminal illness, rather than heeding the specific needs of the individual patient.

The continued supervision of our students' clinical work with patients offered a unique opportunity to check systematically how much progress each student was making and whether or not a change in his attitude was taking place. The most startling observation was the discrepancy between the students' enthusiastic response to lectures and seminars and the persistence of anxiety and bewilderment, when confronted by patients who presented the very same psychological problems the doctors seemed to have grasped fully in theory. Like the medical student, the seasoned practitioner may have taken copious notes with remarkable accuracy during lectures and yet remained quite helpless when called upon to apply his newly gained understanding. To avoid the anxiety mobilized by practice sessions, our postgraduate students welcomed at first our seminars and free discussions during which they were encouraged to talk about the problems they had encountered in their practice. There is also a very real need for instruction in the fundamentals of clinical psychiatry since the majority of the non-psychiatrist physicians knows or remembers little from medical school days.

To be of real value, however, such instruction in psychiatric nosology as well as in basic psychodynamics must be centered around clinical case material. The physician profits most from didactic interviews which give him repeated opportunities to experience for himself "how it's done." He has to be shown how to approach his patients' personality problems and how to deal with their complaints. The physician is quite justified in his critical comment that he has been told once too often in the past that he ought to take more time to "listen" to his patients in order to learn more about them as suffering human beings.

Our experience has taught us that the physician is too preoccupied and too unprepared psychologically to know what he is listening to, or what to do with the material he has just heard.

We have tried over the past three years to change the structure of our course in order to meet these needs on the part of the practitioner as best we can. Formal lectures by attending and liaison psychiatrists in the Department have been reduced from 25 to 14; among these lectures the space given to psychopharmacology has been tripled. Two entire mornings are devoted to demonstrations of hypnotic technique and a discussion of indications and hazards of the use of hypnosis in medical practice, in view of the widespread interest of hypnosis in recent years. The psychological meaning of symptom formation and the dangers in "symptom healing" are presented with clinical illustrations.

The time devoted to demonstrations of initial interview techniques and the number of patients chosen from the medical, diabetic, thyroid, myasthenia gravis and various other clinics has been doubled. These didactic interviews are limited to 25 minutes in order to approximate conditions prevailing in the general practitioner's office practice as much as possible. Rarely ever does a practitioner fail to be amazed at the amount of pertinent material one is able to gather in such a relatively short time. This is all the more important because of the general observation that the physician uses lack of time as his most common excuse for not paying attention to the emotional side of his patients' problems. He also has become accustomed to thinking in terms of 45 minutes or hourly sessions as the minimal time requirement in any type of psychotherapy.

Probably the most significant and difficult task for the instructor of such postgraduate students is the one pertaining to the limitations of the practitioner with regard to "the practice of psychotherapy." Many physicians who seek such training find it hard to accept these limitations. They react to this frustration in a variety of ways. There is the physician who is bitterly disappointed that he is not being taught to handle everything or very nearly every psychiatric disturbance and emergency. He may want to venture out despite all warnings, and "see for himself" what he can accomplish with a patient who is best referred to a specialist. Another physician may react with disappointment and discouragement when told that his function is supportive and not analytic, and he may feel that this type of psychotherapy is not going to accomplish as much for his patients as he had hoped. Actually these physicians react to the narcissistic hurt of being "relegated" to the role of practicing "minor psychiatry."

Eagerness and almost stormy enthusiasm at the very beginning of the course must be given particular attention and must be handled with great delicacy. It is not difficult to sense that oppositionalism and resentment against the psychiatrist lie very close to the surface. Since we are not called upon to treat our student physicians, we have to rely on our ability to arrive at correct evaluations of a student's personal problems, as revealed by his overall behavior in

the different phases of the course. In this respect, our experiences with one young physician were particularly instructive.

He was an alert, aggressive, quick-thinking man in his thirties who during the screening interview as well as on the written application had expressed a genuine desire to learn more about the handling of emotional aspects in his patients, and who had also stressed the fact that a very high percentage of his patients who had problems such as of infertility, showed obvious signs of psychic disturbance. He appeared poised and extremely self-confident. A brief inquiry revealed that he had a very large practice. He had a charming, outgoing quality, a ready smile, and he seemed genuinely interested in his patients.

We were all the more surprised when he became a problem student almost from the beginning of the course. He was argumentative, hostile, on occasion quite tactless during group discussions, and excessively anxious in his approach to the first patients assigned to him. He expressed great concern about possibly making errors in dealing with patients. He said that he had trained himself to shut his mind to anything his patients might say that did not particularly concern the obstetrical or gynecological condition. He made it a point to tell us that he had no knowledge or experience whatever in the field of psychiatry, and that he was ignorant about terminology, nosologic classifications, psychodynamics, and therapeutic technique. He volunteered the information that he had used words such as "immature" and "narcissism" in his conversations with colleagues and patients without really knowing their meaning.

It became quite apparent from the start of individual supervision that his fear about the procedure in handling patients with emotional problems was equalled by a strong desire to question and direct them. In a rather aggressive, impatient and naive manner, he demanded as specific a guide as possible to achieve his goal. He asked for rules and regulations without any specific reference to a particular situation in regard to a patient. When these rules of thumb were not forthcoming in our seminars, he demanded lists of books which he wanted to consult in order to be prepared to handle any of the patients coming to him in the future. His ultimate goal was to learn how to handle each and every patient, to investigate his problems, to understand the dynamics and to solve them—all of this to be achieved in one interview. It was characteristic of him to ask in his very first supervisory session: "How does one finally terminate treatment?" His total manner expressed impatience and dissatisfaction because we were unable to pass on to him the secret knowledge that would enable him to "cure" a patient in one simple interview.

His anxiety increased when his first patient told him that he was playing down the seriousness of her difficulties with her husband and that she did not appreciate his taking these problems so lightly. This offered an opportunity to bring out his feelings of inadequacy in any situation in which he could not offer substantial advice or help. He was amazed at the statement that he could not be expected to have all the answers to all his patients' problems. The hazards of gross and clumsy reassurance were discussed with him, as well as some of the reasons why his patients' demands for help and their searching questions

might be a threat to him. The entire issue of limited goals in psychotherapy was brought up which at first added to his disappointment. The fact that we may have to be satisfied with less than a "cure" seemed unacceptable to him at first. He was also deeply troubled by the discrepancy between the "looks of the patient" from which, as he put it, "no one would ever guess that she was very sick," and the many areas of disturbance revealed by the material elicited from her. It was hard for him to understand how a person "appearing so well integrated on the outside" could be really sick emotionally.

A group discussion in one of our seminars pointed up his personal problems and their nature very sharply. Another doctor had broached the subject of how much to tell members of a family regarding the nature and seriousness of psychiatric illness, when he suddenly took the floor to give an example of his own. He reported that he had been consulted by the twelve-year old son of a schizophrenic patient who had been admitted to an institution. The boy wanted to know from the doctor whether this illness was hereditary and whether he was in danger of becoming mentally ill himself. The doctor now asked how we would have handled the case. He was told that he had to take into consideration certain important psychological elements that pertain to a boy that age, such as feelings of guilt toward the parent. Behind the perfectly rational question there were hidden such infantile preoccupations as "Am I bad?," and "Am I going to be punished for having been bad?" It was also pointed out to him that to the best of our present knowledge, schizophrenia is not a hereditary illness, and that the answer to the boy should have been reassuring to the effect that his mother's illness in no way affected his own chances for a healthy mental future.

At this point the doctor interrupted in a state of agitation with the shouted remark: "All right, so far for the soft-soaping of the boy. Now what about the truth?" He was calmly told that this was indeed the biological and psychological truth, and he was then given an opportunity to vent his own anxieties about the issue of heredity and mental illness. It became quite apparent that this doctor labored under a very special anxiety, possibly caused by experiences with mental illness in his own family. But this issue was of course by-passed and instead a free and lively discussion of the case in point was encouraged and carried through. This incident was the turning point in this physician's attitude towards the psychiatric instruction as well as towards his patients. Within the next several months he underwent a remarkable change, and when Dr. Lawrence Kolb came to The Mount Sinai Hospital to spend a week as visiting professor there, he chose this physician as a fine example of a student in the course who appeared to have grasped the meaning of psychiatry. Dr. Kolb based his conclusions on the manner in which the student handled himself during the case presentation and the ensuing discussion of clinical material.

Indeed, his defensive and aggressive manner had disappeared and he was quite at ease now while discussing his patients' emotional problems, showing a great deal of understanding and compassion.

Some time later we obtained the information that this doctor-student's problems centered around his reactions to a case of mental illness in his own family. His brother had been mentally ill and institutionalized for years.

It is a most rewarding experience for the teacher to observe the development of a true understanding of his patient's emotional needs within the student who learns at the same time more about himself and his own reactions to the patient's demands and questions. At times we have the good fortune to see in statu nascendi the acquisition of skill and judgment.

The following example may serve to illustrate this point: One of the doctors had read through his patient's chart before seeing her. He was impressed by the fact that she had been coming to the clinic for several years and that despite this, she was still very disturbed. Until then, he had not accepted the fact that some patients can only be supported and may be in need of such support for many years. As he put it: "I felt that more could be done. My overall attitude to psychiatry and my feelings about what could or should be done were extremely confused. I had no clear conception of the structure of the therapeutic relationship from a short or long-term point of view. I fluctuated between analytic, behavioristic, rational and hypnotic schools." The doctor could not understand why the specific patient had been permitted to enter a marriage which, as he saw it, "was doomed from the start," and why it had been allowed to continue with the tacit encouragement of the clinic. "I did not understand then that as poor as the relationship was, it was the only one she had; that as much as she appeared to hate it, it seemed to provide her with a link to reality and another person. I felt that a bad relationship should be ended and asked my patient why she continued it, if it was as bad as it seemed. I feel that my indirect encouragement made her decide to terminate the relationship. In this respect, my attitude was opposite to that of her previous therapist. Looking back, I see that I did not investigate any possible positive aspects of the marriage, and I think my present attitude would be to investigate further before reacting as strongly as I did."

Such a modified attitude has indeed come about in this physician through continued clinical work and particularly through discussions which focussed on his patient's reactions to his first interviews with her. He described his initial interview with her as "a tense affair, and I went at it like a bull in a china shop, firing questions about her sexual problems which I had gleaned from her chart. She showed some surprise. There were moments when I felt very desperate as I became aware of my patient's despair. I felt confused and quite inadequate about my ability to steer her through her troubled times. I felt she needed an expert, and that I was not one."

Gradually, the doctor came to experience the importance of a kind, accepting attitude on his part for this patient, and of the inherent dangers in moralistic responses and impatient directions. Several months later, he had grasped and experienced the true meaning and therapeutic significance of transference in his work with his patient. He made a sound suggestion that this patient be assigned to a therapist who was in a position to continue treating her for several years more. He said: "Being changed from one therapist to another each year may prevent her from building and experimenting with one relationship. Thus, she is not enabled to generalize on the basis of this one trusted contact."

When this physician started our course, he had an excessively optimistic atti-

tude "that everyone could be normalized, provided one worked hard enough at it. The whole idea of limited goals in therapy had seemed distasteful to me and defeatist. Work with this patient was at first painful and anxiety-provoking to me." To relinquish his hopes "for a complete cure," to renounce his omnipotent phantasies for a magic solution to his patient's problems, and to learn to accept his own lack of control over the patient's reactions, resulted in the kind of change in his overall attitude that we always had in mind. Through his clinical experience he had begun to realize the importance of what he had formerly deprecatingly called "merely supporting" therapy in a patient whose object relations are shallow and whose hold on reality is tenuous.

A pilot seminar for doctors who had taken the basic course in Fundamentals of Psychiatry in 1959 and 1960 was initiated in 1961. The encouraging, perhaps extraordinary fact was that the idea for the seminar had originated with our students. For them it was to be a continuation of the course's fruitful discussions, a meeting place where they could air the diagnostic and therapeutic problems they were facing in everyday practice. For us this follow-up seminar which is open to all doctors who have completed the course of basic instruction, offers in our opinion, the only means to really evaluate the effectiveness of our teaching program. This seminar takes place biweekly and lasts from two to three hours each time. The doctors are encouraged to present in some detail their recent experiences with their own patients, both successful and unsuccessful. These case presentations alternate with material presented by the instructor who dwells on specific points of technique and asks each member of the group how he would have handled these situations in his own practice. Continuous case presentations extending over several months are an integral part of the structure of the seminar. We are able, therefore, to dispense with questionnaires whose value appears doubtful to us since we must expect that in many instances the former students' self-evaluation is quite inaccurate and unreliable. The seminar offers us direct observation of the doctor's attitude toward his patients. A further cross check is offered by the instructor's consultation with the students' patients or their families.

An example in point is the self-evaluation of one of our students who said: "I don't feel there is any change in the way I practice, but I can utilize some of the things I have learned in the course." Two of his long-term patients, whom he had referred for psychiatric consultation, when interviewed by a psychiatrist not connected with this course, told him that they had noticed an appreciable change in the doctor's attitude, which they expressed in terms of his greater kindness, patience and interest.

One striking observation was that the range of problems presented by the physicians far exceeded what might be considered the classic psychosomatic problems, such as the diabetic patient, the hypertensive, the peptic ulcer patient, and a case of neurodermatitis. The practitioners saw patients, and families, who came to them for help with such problems as artificial insemination, male and female homosexuality, polymorphous perversions, out-of-wedlock pregnancy in emotionally disturbed adolescents, and delinquent behavior in teenagers.

A general practitioner after having attended our course commented: "One important aspect of the experience obtained was a recognition of emotional disorders which require the immediate attention of the specialist. Throughout the year, it is quite surprising to see the number of schizophrenic breakdowns, severe depressions, suicidal motivations and attempts and severe anxiety states that one can recognize and help by prompt referral. Having seen the methods of treatment of these illnesses, one is no longer diffident or unsure in recommending the proper course to be taken. Of all the postgraduate courses that I have taken in the various specialties of medicine, none has given me greater knowledge and greater assistance in caring for sick people than the course in psychodynamics."

The validation of a specific teaching method in medicine is traditionally based on 1) examinations, 2) a check on the student's clinical performance in a hospital setting, and 3) the student's own verbal or written reactions to a specific teacher, course or methodology.

So far, evaluations of postgraduate courses in the fundamentals of psychiatry have leaned rather heavily on personal pronouncements by the participating physicians. After the Minnesota experiment a fairly extensive follow-up was done, based entirely on oral communications or letters from the former students. Most of these physicians felt that there was a change in their relationships with their patients.

With respect to such self-appraisals a rather amusing note was contributed by the answer to the question whether our students had felt a decisive change within the nine-month period of the course or later on during the follow-up seminar. Four out of eleven agreed with the statement of one, who said that he was left "high and dry" and needed the follow-up seminars, while the other seven believed that the course itself had been sufficient to bring about such a change. The spokesman for those seven was a doctor of strong positive convictions whose over-optimism and hyperactive approach to his patients' problems had worried us a great deal and still continued to be a source of concern during the follow-up seminars. Self-evaluation in this student again proved to be misleading and fallacious.

We never considered formal examinations as a measure of results, since our primary goal was not to pass on to the physicians a compendium of theory and practice of psychotherapy to be memorized and rigidly followed. This would encourage a superficial indoctrination with rules of thumb. A true understanding of the intricacies of psychodynamics takes years of study and experience.

We then come to a third means of evaluating results, the check on the clinical performance of the student. This approach we indeed find valuable. It offers several built-in controls. We are no longer dependent on a student's "testimonial" in which he expresses his satisfaction with the course, its instructors and how much he has benefited from it. It is the clinical test only which enables the instructor to judge whether his students have indeed arrived at a change in attitude towards their patients, whether this change has been substantial or small, and whether it has been a fleeting phenomenon rather than a lasting transformation. The supervised clinical work during the course itself offers such op-

portunities, and the follow-up seminar provides an even more rigorous check on who has and who has not gained from his exposure to nine months of clinical instruction.

It could well be that wishful thinking has with increasing frequency crept into some of the statements we have read over the past several years and which have been accepted by some authors as self-evident truths. Among these belongs the assumption that the practicing physician due to his professional experience and maturity will be better able than the medical student to benefit from psychiatric instruction in a highly concentrated form, and that we therefore do not have to expect to trigger off emotional reactions within the student-physician. But is this really a true statement of observed fact? We are familiar with transference problems arising in medical students who force their professor into the role of therapist and who expect his love and active assistance in their personal difficulties. We see that psychiatric residents may be hindered by their unresolved conflicts which lead to unproductive discussions, dominated by emotional harangues directed at the entire field of psychiatry or specific schools of psychoanalytic thought, while all the time they are fighting authority. We are actually in a much better position with the psychiatric resident to whom we can suggest therapy and possibly refer for his personal psychoanalysis. We are not in the same position with the non-psychiatrist physician who comes to us for postgraduate training. Balint tried to solve this dilemma by adding regular group psychotherapy sessions to his course of instruction (3). Grodzicki has pointed out the limitations of such an attempt at a compromise which stresses training, but offers at the same time minimal analytic treatment in a group setting (6).

We have found that each year there is at least one doctor in the group who shows major transference problems from the very beginning of the course, becomes involved in long-winded arguments during seminars and who constantly challenges his instructor during individual sessions. Our way of handling these delicate transference issues has been to steer clear of the role of therapist as much as possible. Instead we may try to help the doctor to see that we are aware of his dilemma and that it is not a surprising one. We may point out the magical element in all illness, and the counter-magic invested in the healer. We may mention the possible origin of rescue phantasies as a motive underlying the choice of medicine as a profession, and we will illustrate it with some examples. The physician is reminded of those points in our talks on the doctor-patient relationship which dealt with the doctor's striving for authority and recognition and for blind obedience on the part of his patients as means of gratifying his unconscious striving for omnipotence. Contrary to his own inner needs, immediate therapeutic results cannot be expected. This, however, is precisely what so many of our colleagues who come to us for this kind of training expect—to be given the magic clues to the technique of treating all emotional problems encountered among their patients.

When teaching the fundamentals of clinical psychiatry and psychodynamics, whether to medical students, psychiatric residents, or non-psychiatrist physicians, we must be prepared for a "reverberation within the student and this leads

to disturbances and difficulties" (7). In demonstrating mechanisms of defense within the ego, such as repression and isolation, we are on potentially dangerous ground since these same defenses had to be utilized by our students in order to attain a professional attitude of objectivity and emotional detachment from their patients. Thus, the postgraduate psychiatric re-education of the physician threatens his ego by attacking the delicate balance of long-established defenses.

An illustration in point is the remark made by a former student of ours who is now attending the seminar. He said that he realizes the change because he can now allow a patient to talk without feeling the need to interfere. He realizes that all sick people have anxieties. He sees that he can now, for the first time, permit himself to become exposed to his patients' anxieties "without being affected by their upset" and without generating counter-anxiety within himself. He attributed this change to the discussion of his own fears and anxieties in relation to the patients during the supervisory interviews. He felt that the repeated opportunities to ventilate his own reactions to problems presented by his patients were probably the most valuable part of the course.

Eight out of eleven doctors attending the follow-up seminar agreed that such a chance to bring out their personal apprehensions and uncertainties in group discussions was most helpful. We will not be surprised therefore to find that lengthy introductory lectures about psychodynamic theory, ego and libidinal development hurt rather than help in the pursuit of our teaching goals. Such seminars and lectures, to be effective, have to be structured around clinical material which permits the utilization of patients known to the student to illustrate the dynamic forces and their interplay in the individual case.

SUMMARY

The course of instruction in Basic Psychiatry for Medical Practitioners at The Mount Sinai Hospital, New York, has taught us a good many things during its four-year existence. Our emphasis on clinical material around which the whole structure of the course has been built is even greater today than it was at the start. The physician needs the experience of working with a live patient, if he is to be helped to overcome his own anxieties, engendered by problems which he has trained himself all along to ignore. Each year the time set aside for the practice of initial interview technique has been increased. These didactic interviews provide a valuable experience, since they offer the practitioner an opportunity to observe an instructor obtain relevant information in a 20 to 25 minute session.

We have become more convinced than ever that series of lectures and seminars do not contribute enough to achieve our teaching goal to bring about in the practitioner a change in attitude and outlook toward all his patients. To grasp the significance of the doctor-patient relationship is of equal, if not greater importance to the physician, than the acquisition of psychiatric nosology. While our course offers a great deal of formal instruction, its format facilitates the integration of theory into the overall clinical framework. We have tried to combine formal instruction with actual training in its practical application.

A follow-up seminar, which is now in its second year, has become an important

means to evaluate the effectiveness of our teaching program. It has freed us from an exclusive reliance on a student's self appraisal. We have found that the follow-up seminar provides a rigorous check on who has and who has not gained from his participation in a nine-month course of clinical instruction.

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Repeat Cesarean Section—Report of 1028 Cases

I. Perinatal Mortality

II. Post-section Scar Separation and Rupture

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This report of the experience of The Mount Sinai Hospital with repeat cesarean section seems appropriate in view of current controversy in the management of the post-section parturient. It is hoped that an analysis of this large series of repeated cesarean sections may be of some statistical and clinical value. Particular attention will be given to two facets of the problem—perinatal mortality associated with repeat section and disruption or rupture of the previous uterine scar found at repeat operation.

Although post-cesarean vaginal delivery will not be discussed in this presentation, its incidence on the private and ward services is shown in Table I. There were 1137 previous cesarean sections. Of these, 109 (9.6%) were delivered vaginally. On the private service there were 814 previous sections. Forty-one (5.0%) were delivered from below. On the ward service 68 (21.1%) were delivered vaginally following 323 previous sections. All the uterii were explored following vaginal delivery and the previous uterine scars were found to be intact.

In the first eight years of the Obstetrical Department's existence (1953–1960) there were 36,853 deliveries of which 2047 (5.6%) were terminated by the abdominal route. There were 1019 (2.8%) primary and 1028 (2.8%) repeat cesarean sections. The latter operation gradually, over the years, became somewhat more frequent than the primary operation (Table II). Twelve sets of twins were born by repeat section. There was no maternal mortality in the series of patients upon whom repeat section was performed. One patient died, however, after a primary section. She was a primigravida, already ambulatory, who died of a pulmonary embolus 31 hours after operation. This gives a total maternal mortality associated with cesarean section in this eight year period of .049 per cent or 4.9 per 10,000.

The number of complications in the prenatal period that influence the perinatal mortality in repeat section preclude an accurate picture of the fetal loss associated with this operation, per se. Therefore, two main categories will be analyzed. In the first group, complications such as premature separation of the placenta, placenta previa, toxemia and premature labor dictate an emergency repeat section forcing the obstetrician to terminate pregnancy before he had planned to do so. The fetal loss is high and approximates the perinatal loss in primary cesarean sections under similar conditions. The second group is com-

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prised of patients who had uncomplicated elective repeat sections in which the surgeon could select the time of operation uninfluenced by complicating factors. It is in this group that the true relationship of perinatal mortality to repeat section can be determined accurately. Although repeat section in the pregnant woman with diabetes is not entirely an elective procedure, the accepted manage-

TABLE I

Vaginal Delivery Following Previous Section

Year	Private			Ward			Total		
	Prev. Section	Vag. Del.	%	Prev. Section	Vag. Del.	%	Prev. Section	Vag. Del.	%
1953	61	4	6.5	21	5	23.8	82	9	10.9
1954	91	5	5.5	27	7	25.9	118	12	10.2
1955	109	4	3.7	33	2	6.1	142	6	4.2
1956	123	4	3.3	62	12	19.4	185	16	8.6
1957	107	8	7.5	37	5	13.5	144	13	9.0
1958	114	6	5.3	45	6	13.9	158	12	7.6
1959	100	6	6.2	43	13	31.0	141	19	13.5
1960	109	4	3.8	55	18	33.3	161	22	13.7
Total	814	41	5.0	323	68	21.1	1137	109	9.6
Repeat Sections	773			255			1028		

TABLE II

Total Cesarean Sections—Primary and Repeat

Year	Deliveries	Total Sections	Primary Sections	Repeat Sections
1953	2779	157 (5.7%)	84 (3.1%)	73 (2.6%)
1954	4279	246 (5.8)	140 (3.3)	106 (2.5)
1955	4630	290 (6.3)	147 (3.2)	143 (3.1)
1956	4829	297 (6.2)	129 (2.7)	168 (3.5)*
1957	4920	260 (5.3)	129 (2.6)	131 (2.7)*
1958	4932	283 (5.7)	138 (2.8)	145 (2.9)*
1959	5300	241 (4.5)	118 (2.2)	123 (2.3)*
1960	5184	273 (5.3)	134 (2.6)	139 (2.7)*
Totals	36,853	2047 (5.6%)	1019 (2.8%)	1028 (2.8%)

* Repeat sections exceeding primary sections.

ment being delivery several weeks before term, repeat section in the diabetic is included in the elective repeat section category.

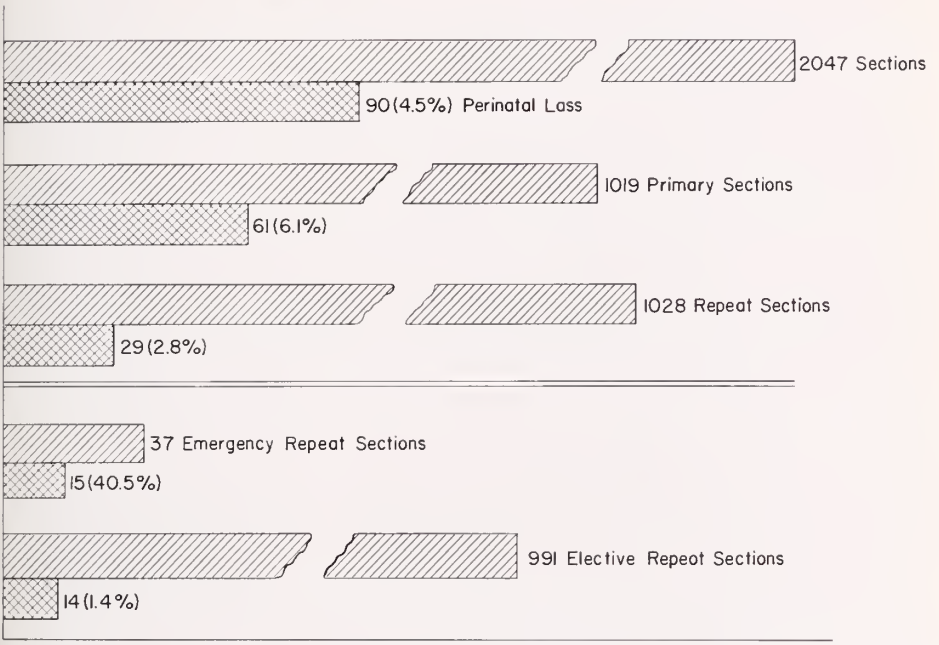
The overall perinatal mortality in the 2047 sections (Table III), both primary and repeat was 90 (4.5%) or 45 per 1,000. The uncorrected perinatal loss in 1019 primary sections was 61 (6.1%) and in 1028 repeat sections 29 (2.8%). Analyzing the repeat sections further, it is noted that there were 37 emergency repeat sections with a perinatal loss of 15 (40.5%) and 991 elective repeat sec-

tions in which the perinatal loss was 14 (1.4%). These perinatal loss figures are uncorrected for immaturity and includes all liveborn or stillborn infants weighing 400 Gm or more and all neonatal deaths within the first 28 days of life, regardless of the length of gestation.

Table IV shows the fetal loss according to weight in the emergency, elective, and total repeat section categories. There were 37 emergency repeat sections. Six (16.2%) infants were mature (2500 Gm or more) and 31 (83.8%) were premature infants. Of the latter, 4 (10.8%) weighed between 400 and 999 Gm (immature), 4 (10.8%) weighed between 1,000 and 1,499 Gm, 14 (37.8%) weighed between 1,500 and 1,999 Gm, and 9 (24.3%) between 2,000 and 2,499 Gm. It will be noted that the perinatal mortality in this premature group is extremely high with a fetal loss of 13 in 31 premature infants, an incidence of 41.9 per cent. Of the 6 mature infants, 2 (33.3%) were lost. The overall perinatal mortality in the 37 emergency repeat sections is 15 (40.5%). Eliminating the 4 immature infants (400–999 Gm) the corrected perinatal mortality in this emergency repeat section group for all infants over 1,000 Gm, 11 (29.7%), is still very high.

TABLE III

Perinatal Mortality in Total, Primary and Repeat Sections*



* Includes all stillbirths and all neonatal deaths within the first 28 days of life weighing 400 Gm or more regardless of period of gestation.

Analysis of the fetal loss in elective repeat sections shows a wholly different picture. At The Mount Sinai Hospital the operation is usually performed at some time after the 38th week, during a time of the day when there is optimum

coverage by residents, nurses and laboratory technicians. There were 991 elective repeat sections producing 929 (93.8%) mature and 62 (6.2%) premature infants. The weight distribution of the prematures was as follows: none in the 400 to 999 Gm group, 1 (0.1%) in the 1000 to 1499 Gm group, 4 (0.4%) in the 1500–1999 Gm group and 57 (5.7%) in the 2000 to 2499 Gm group. It is to be noted that 14 (1.4%) infants were lost in the 991 elective repeat sections. Ten (1.1%) of the 929 mature infants were lost and only 4 (6.4%) of the 62 premature infants. All five infants weighing less than 2000 Gm survived. One infant, (twin B) weighed 1446 Gm, twin A was a mature infant. Another infant presented as a transverse lie and weighed 1640 Gm. Still another infant weighed 1840 Gm. Another weighed 1950 Gm and the fifth infant weighed 1960 Gm at

TABLE IV

Weight of Infant and Fetal Loss at Repeat Section

Weight Grams	Emergency Repeat Section				Elective Repeat Section				Total Repeat Section			
	No.	%	Fetal Loss	% Loss	No.	%	Fetal Loss	% Loss	No.	%	Fetal Loss	% Loss
400–999	4	10.8	4	100.0	0	0	0	0	4	0.4	4	100.0
1000–1499	4	10.8	3	75.0	1 (Twin B)	0.1	0	0	5	0.5	3	60.0
1500–1999	14	37.8	5	35.7	4	0.4	0	0	18	1.7	5	27.8
2000–2499	9	24.3	1	11.1	57	5.7	4	7.0	66	6.4	5	7.6
Total Prematures	31	83.8	13	41.9	62	6.2	4	6.4	93	9.0	17	18.2
2500 or more	6	16.2	2	33.3	929	93.8	10	1.1	935	91.0	12	1.3
Total	37		15	40.5	991		14	1.4	1028		29	2.8
Over 1000			11	29.7			14	1.4			25	2.4

38 weeks. In four of the five infants weighing less than 2000 Gm, therefore, there was gross misjudgment of the fetal weight on the part of the obstetrician.

As noted previously, there was a total of 1028 repeat sections with a perinatal mortality of 29 (2.8%) corrected to 25 (2.4%) by eliminating the four immature fetuses. Of the 935 (91.0%) mature births, 12 (1.3%) infants were lost and of the 93 (9.0%) premature deliveries 17 (18.2%) infants were lost. Analyzing the 93 premature births according to weight and fetal loss, it is noted that 66 (6.4%) weighed between 2000 to 2499 Gm with a fetal loss of 5 (7.6%); 18 in the 1500 to 1999 Gm group with a loss of 5 (27.8%); 5 in the 1000 to 1499 Gm group with a loss of 3 (60.0%) and 4 immature infants in the 400 to 999 Gm group with a 100 per cent loss.

There were 93 (9.0%) premature infants delivered in the entire series of repeat sections, 31 (83.8%) as a result of an emergency repeat operation when the

surgeon was forced to operate and had no control over the weight of the baby. The repeat elective section was performed at the choice of the obstetrician, usually within two weeks prior to the estimated date of delivery. The remaining 62 (6.2%) premature infants resulted from the obstetrician's error in estimating the fetal weight. The literature lays great emphasis on this error. To circumvent such misjudgment many authors even suggest surgery only after labor has started. This maneuver may eliminate prematurity due to erroneous timing of the operation by the surgeon but it defeats the purpose of an elective repeat section, *i.e.*, the avoidance of labor to lessen the chance of rupture of the previous scar.

Table V shows the causes of the perinatal mortality in the various weight categories in both the emergency and elective repeat sections. Of the 15 babies lost in the emergency group, anoxia accounted for 10 distributed as follows: premature separation of the placenta 5, placenta previa 3, prolapsed cord with premature labor 1, and 1 ruptured uterus. A previous classical scar from a cesarean section performed several years before at another institution ruptured at 26 weeks. There were also three cases in which no fetal heart was present on admission. One of these cases with previous extensive myomectomies had a complicating hypofibrinogenemia; another had had two previous sections and was in early labor. Since tubal ligation was planned, the uterus was emptied from above producing an immature stillbirth. The third patient, with diabetes, went into premature labor at 32 weeks of gestation, and her baby weighing 1930 Gm died within 12 hours. There were four patients in this emergency category who had premature labors. Two of them have been mentioned earlier. One of the remaining two had had one previous section and delivered an infant weighing 1920 Gm as a result of premature labor. The infant died of hemolytic disease during an exchange transfusion. The other infant weighing 1588 Gm, the product of another premature labor, died in 18 hours of hyaline membrane disease. Its mother had had two previous cesarean sections.

Of the 14 infants lost in the elective repeat section group, 8 had abnormalities incompatible with life. Two of these 8 cases were associated with maternal diabetes. One infant weighing 4050 Gm died of hyaline membrane disease, one weighing 3330 Gm (twin A) died at two weeks from a septicemia of unknown origin, and another weighing 3714 Gm died within 24 hours of atelectasis and pneumonia. Another stillborn infant weighing 2420 Gm was delivered by a fourth cesarean section for diabetes. No fetal heart had been present on admission. Another diabetic mother bore a mature infant weighing 4050 Gm and dying in 24 hours from cyanosis and apnea. This was her fifth repeat section for diabetes. Still another diabetic was delivered of a 2030 Gm infant who died of atelectasis in 15 hours.

There were 49 diabetic mothers who were delivered by repeat cesarean section. One was in the emergency section group (premature labor at 32 weeks of gestation) and 48 were in the elective cesarean repeat group. Six infants were lost. Two (2800 Gm and 2360 Gm) of these were abnormal infants; one (2420 Gm) had no fetal heart present on admission; one (4050 Gm) died of cyanosis

TABLE V

Causes of Perinatal Mortality at Repeat Section

Cause	Emergency Section (15)					Elective Section (14)					Total
	Grams 400–499	1000–1499	1500–1999	2000–2499	2500 or more	400–999	1000–1499	1500–1999	2000–2499	2500 or More	
Prem. Sep. Placenta (Anoxia)	1 (No F.H.)	2 (N) (N)	1 (N)	1 (N)							5
Previa (Anoxia)	2 (N) (SB)				1 (N)						3
Prolapsed Cord (Anoxia)			1 (PL) (SB)								1
Rup't. Uterus through Prev. Class. Scar (Anoxia)					1 (SB)						1
No F.H.—2 Prev. Sections Ligation Planned	1 (PL) (SB)										1
No F.H.-Prev. Extensive Myomectomies Hypofibrinogenemia		1 (SB)									1
Diabetes (Mother)			1 (PL) (N)						1 (No F.H.)	1 (N)	3
Hemolytic Disease			1 (N)								1
Abnormalities									2 (N) (N) Diabetic	6 (5 SB) (1 N) (1 Diabetic)	8
Septicemia (Twin-A) (Cause Unknown)										1 (N)	1
Atelectasis-Pn.									1 (N) Diabetic	1 (N)	2
Hyaline Memb. Dis.			1 (PL) (N)							1 (N)	2
Total	4	3	5	1	2	0	0	0	4	10	29

and apnea; one (2030 Gm) died of atelectasis and the one (1930 Gm) in the emergency section group died in 12 hours (cause unknown).

In summary, Table VI depicts the total fetal loss encountered in 1028 repeat cesarean sections, both emergency and elective. Eight infants had lethal abnormalities, two of these were the infants of diabetic mothers. There were four ad-

TABLE VI

Causes of Perinatal Mortality at Repeat Section (Total)

Cause	Grams 400–999	1000–1499	1500–1999	2000–2499	2500 or More	Total
Prem. Sep. Placenta (Anoxia)	1(SB)	2(N) (N)	1(N)	1(N)		5
Previa (Anoxia)	2(SB) (N)				1(N)	3
Prolapsed Cord (Anoxia)			1(PL) (SB)			1
Rupt. Uterus through Class. Scar (Anoxia)					1(SB)	1
No F.H.—2 Prev. Sections Ligation Planned	1(PL) (SB)					1
No F.H.—Prev. Extensive Myomectomies		1(SB)				1
Hypofibrinogenemia						
Diabetes (Mother)			1(PL) (N)	1(No F.H.)	1(N) Apnea	3
Hemolytic Disease			1 (N) (Exch. Transf.)			1
Abnormalities				2(N) (N) (1 Diabetic)	6 (5 SB) (N) (1 Diabetic)	8
Septicemia (Twin A) (Cause Unknown)					1(N)	1
Atelectasis—Pn.				1(N) Diabetic	1(N)	2
Hyaline Memb. Dis.			1(PL) (N)		1(N)	2
Total	4	3	5	5	12	29

P.L.—Prem. Labor; N—Neonatal; SB—Still Birth.

ditional deaths associated with maternal diabetes. Eight infants were lost associated with placenta previa and premature separation of the placenta. Two were lost because of hyaline membrane disease. One was lost from a prolapsed cord and one as a result of a ruptured uterus. One died from hemolytic disease during an exchange transfusion. Two infants were dead before section. One (twin A) died of an unknown septicemia and one died of atelectasis.

Table VII shows the indications for the emergency and elective repeat sections

with the fetal loss and their weights. Of the 37 emergency repeat sections, 15 were performed for placenta bleeding; 11 for premature labor, with the remaining 11 cases being operated upon for toxemia (3), history of previous fetal deaths from placental insufficiency (3), isoimmunization (2), hypofibrinogenemia (1), prolapsed cord (1), and ruptured uterus (1). The ruptured uterus occurred in a patient who had had two previous classical sections and one low flap section. Rupture occurred at 36 weeks of gestation through one of the previous classical

TABLE VII

Indications for Repeat Section and Fetal Loss

Indication	No. of Cases	Fetal Loss					
		Grams 400–999	1000–1499	1500–1999	2000–2499	2500 or more	Total
A. Emergency Repeat Section							
Placenta Previa	8	2	0	0	0	1	3
Prem. Sep. Placenta	7	1	2	1	1	0	5
Prem. Labor	11	1	0	2	0	0	3
Isoimmunization (Rising Titers)	2	0	0	1	0	0	1
Toxemia	3	0	0	0	0	0	0
Hypofibrinogenemia	1	0	1	0	0	0	1
Prolapsed Cord	1	0	0	1	0	0	1
History of Prev. Placental Insufficiency	3	0	0	0	0	0	0
Ruptured Uterus	1	0	0	0	0	1	1
Total	37	4	3	5	1	2	15
B. Elective Repeat Section							
Prev. Section Including Diabetes	991	0	0	0	4	10	14
Total	1028	4	3	5	5	12	29

scars and resulted in extrusion of the dead fetus and the placenta into the abdominal cavity.

The indication for the 991 elective repeat sections was one or more previous sections including maternal diabetes.

The anesthesia usually employed was a spinal anesthetic given by expertly trained anesthesiologists. Its effect on the fetus was negligible and we believe anesthesia did not influence the perinatal mortality. Inhalation anesthesia was administered infrequently and only when there was a contraindication to the use of spinal or strong objection to a spinal by the patient. Pontacaine (1%) mixed with equal parts of 10% glucose was the agent employed. The dose of pon-

tacaine depended upon the weight of the patient and never exceeded 10 milligrams.

There were 25 cesarean hysterectomies among the 1028 operations. The indications for removal of the uterus were: myomata 6, multiparity 8, excessive bleeding during the operation including broad ligament hematomas 9 (5 of which were associated with previous cesarean scar separations), placenta accreta 1, and 1 rupture of the uterus through a previous classical scar.

In a previous publication on the rupture of the post-cesarean scar, 16 scar dehiscences or ruptures were found in 320 consecutive repeat sections, an incidence of five per cent or one in every twenty repeat sections performed. This represented the first three year period (1953–1955) that the new maternity section of The Mount Sinai Hospital was in operation. Our paper was presented because the incidence of five per cent post-cesarean scar dehiscence and rupture was high compared to the 0.5 per cent to 2.5 per cent incidence reported in the literature.

There was no maternal death and only one perinatal death. This occurred in the only case of true rupture, a catastrophic occurrence involving a previous classical scar in a patient who had had 3 previous sections; 2 classical sections followed by a low segment section. The fetus and placenta had been extruded into the abdominal cavity. It is possible that this high incidence of scar rupture and dehiscence in the first series of repeat sections reported from The Mount Sinai Hospital may have been due to faulty closure techniques, since all the patients involved had had their primary operation at other institutions. In the 708 repeat cesarean sections in the five year period, 1956 to 1960 inclusive, only 7 cases of scar dehiscence were noted, an incidence of one per cent. Almost all of these patients had their previous sections at The Mount Sinai Hospital. Adding these 7 dehiscences to the 15 dehiscences and one case of fundal scar rupture, we find 21 cases of lower segment dehiscence, one case of classical scar dehiscence and one case of classical scar rupture, giving a total incidence of 23 faulty scars (2.2%).

Table VIII represents the salient data in these 23 cases. There was no maternal mortality. Two infants were lost, (Cases 2 and 18). The first, weighing 3003 grams, died because of a rupture through a previous classical scar at 36 weeks of gestation, with the fetus and placenta in the abdominal cavity. The infant in Case 18, an immature (600 Gm) was delivered by emergency repeat section for placenta previa with marked bleeding at 26 weeks' gestation. The first section performed 12 years previously was also for previa and the second miscarriage, 8 years before had a partial previa with manual removal of the placenta and a septic postpartum course.

Six of the 23 cases had 2 previous sections and one patient had 3 previous sections (2 classical followed by a low segment operation). Sixteen patients had only one previous cesarean section.

Six patients had a trial of labor in the present pregnancy. Four of these patients experienced no pain referable to the previous scar and were sectioned only because labor was not progressing satisfactorily. One had sudden acute

TABLE VIII

Analysis of 23 Cases—Postsection Scar Ruptures

	Age	Para	Priv.-ward	No. Sect.	Indication First Section	Type Section Incision	Yrs. Bet. Last and this Section	Prev. Morbid	Labor Now	Scar Pain	Matern. Mort	Fetal Loss	Size of Separation	Procedure	Weight Grams
1	23	1011	W	1	CPD	L.F. Trans.	4	0	Trial	0	0	0	2 cm.	Low flap-repaired	3590
2	32	3033	P	3	Fetal distress	Class Class L.F. Trans.	3 3 2	0	0	Mild abd. pain	0	†	Complete thru class scar	Subtotal hyst. (bleeding)	3003
3	22	2022	P	2	CPD	L.F.-Vert. L.F.-Vert.	1 2	0	0	0	0	0	8 cm.	Low flap-repaired ligation	3350
4	33	2022	P	2	CPD	L.F.-Trans. " "	2 4	0	0	0	0	0	8 cm.	Subtotal hyst. (bleeding)	2730
5	24	2022	W	2	?	L.F.- " " "	5 4	0	Early	0	0	0	4 cm. Elbow	Subtotal hyst. (sterilization)	3420
6	28	1001	P	1	CPD	L.F.- "	2	0	0	0	0	0	4 cm.	Low flap-repaired	3900
7	25	2001	P	2	"	L.F.-Vert. " "	1 1	0	0	0	0	0	4 cm.	Low flap- " ligation	3300
8	34	1011	W	1	CPD	L.F.-Trans.	2	0	Trial	Sudden acute	0	0	6 cm. Elbow	Low flap-repaired	3480
9	34	1001	P	1	Fetal distress	" "	2	0		Exquisite tenderness	0	0	6 cm.	Subtotal hyst. (bleeding)	3170
10	32	1001	W	1	CPD	" "	4	0	Mild	0	0	0	Complete	Low flap-repaired	3910
11	35	2002	P	2	Toxemia	" "	6	0	"	0	0	0	5 cm.	Subtotal hyst. (bleeding)	3230

12	32	1001	P	1	Fetal distress	" "	3	0	0	0	0	0	8 cm.	Subtotal hyst. Plac. Previa-bleeding	2760
13	37	1001	P	1	Ablatio	" "	1	0	0	0	0	0	10 cm.	Low flap-repaired	3400
14	31	1001	W	1	CPD	" "	2	0	Trial	0	0	0	8 cm.	" " "	
													Shoulder		2977
15	32	1001	W	1	"	" "	5	†	"	0	0	0	4 cm.	" " "	3019
16	28	1011	W	1	"	" "	4	0	0	0	0	0	2 cm.	" " "	3490
17	32	2112	P	2	CPD	L.F.-Trans.	3	0	0	0	0	0	4 cm.	Low flap-repaired	3560
						" "	3							ligation	
18	37	1021	P	1	Previa	" "	12	?	2 hr.	0	0	†	Fetal parts thru scar under bladder	Cesarean-subtotal hyst. Hematoma in broad lig.	600
						Marked bleeding—Previa again at 26 Weeks									
19	27	1001	P	1	CPD	L.F.-Vert.	3	?	0	0	0	0	6 cm.	Low flap-repaired	4430
20	40	1011	P	1	Trans. lie.	L.F.-Trans.	2½	0	0	0	0	0	4 cm.	" " "	3150
21	27	1101	P	2	Ablatio	" "	2	0	0	0	0	0	6 cm.	" " "	2800
						" "									
22	28	3225	W	1	Previa	" "	4	?	0	0	0	0	5 cm.	" " "	2690
23	35	5036	W	1	CPD	Class.	2½	0	14 hr. trial	Labor pains	0	0	4 cm placenta under separation	" " " ligation	4210

pain after ten hours of labor, and one patient had exquisite tenderness on palpation of the lower abdomen after six hours of labor. Four patients were admitted in mild labor before repeat section, one complained of mild abdominal pain. Thirteen patients had no labor before repeat section, and the dehiscence was a wholly incidental finding.

Twenty-one patients had previous low segment sections, the transverse incision being employed more frequently than the vertical incision. Two patients had classical scar deficiencies. One had two previous classical sections followed by a low segment operation. The classical scar ruptured at 36 weeks with the dead fetus and placenta expelled into the abdominal cavity. The other classical scar separation was not catastrophic because the placenta under the classical scar prevented complete rupture. The rupture was of the silent type and the infant lived. It is quite apparent that low segment scars do separate. However, one is impressed with the benign nature of the separation. It is not uncommon at operation to see a window of a few centimeters enlarge under the eyes of the surgeon as the bladder is mobilized from the lower uterine segment. These silent dehiscences are discovered only at the time of the repeat section. In spite of a trial of labor and in some cases an extremity protruding through the window, no patient presented herself as an emergency, and only one infant was lost. The infant weighed 600 Gm and was delivered at 26 weeks' gestation because of marked bleeding from a placenta previa. The classical scar ruptures, on the other hand, are usually explosive in nature and present a very serious situation for mother and infant.

The extent of the separation or rupture of the post-cesarean scar varied from 2 cm to complete rupture with expulsion of the fetus and placenta into the abdominal cavity in one of the two post-classical sections involved in scar rupture. Four patients had one or more fetal parts protruding through the separated scar; two had elbows, one had a shoulder, and one (Case 18) had the immature fetus in the intact membranes extruded through the old scar under the bladder. Two of the patients (one with an elbow and one with a shoulder through the scar) had a trial of labor, the repeat sections being performed only because labor was not progressing satisfactorily.

The interval between the last section and the present repeat section varied from 1 to 12 years with only two patients giving a history of previous morbidity following their previous sections.

The fate of the uterus after the repeat section depended upon the age of the patient, her parity, the accompanying bleeding and the condition of the surrounding uterine and broad ligament tissues. In 16 cases the lower segment scar was trimmed and repaired. Five of these had accompanying tubal ligations. There were seven subtotal hysterectomies performed; one patient had 3 previous sections, 3 had two, and 3 had one previous section. All had previous lower segment operations and one had 2 previous classical sections before the low segment section. Five of the seven hysterectomies were done because of extensive bleeding and broad ligament hematomas; a sixth for sterilization and the seventh because of complete rupture with the fetus expelled into the abdominal cavity.

One patient (Case 1) who had a ruptured scar at repeat section in 1953 had a third section in 1956. The scar was found intact and a mature living infant weighing 3370 Gm was delivered.

There seems to be no way of predicting which previous scar will dehisce or rupture for there is no adequate means of evaluating the behavior of the previous uterine scar late in a subsequent pregnancy or labor. Various aids have been suggested to evaluate the strength of a scar after previous section, but they have been of little help. These include post-section hysterography, subjective pain and tenderness on palpation in subsequent pregnancies and labors, history of previous morbidity, vertical rather than transverse low segment incisions and more fastidious techniques in closing the lower segment. Beacham has very adequately summarized our knowledge in predicting the behavior of the post-section scar in subsequent pregnancies, "Even if one knows why, where, by whom, how and when the previous cesarean was performed, one still cannot vouch for the integrity of the scar, even though the post-operative course was smooth" (2).

SUMMARY

1. An analysis of 1028 repeat cesarean sections is presented with special emphasis on perinatal mortality and post-cesarean scar ruptures and dehiscences encountered during pregnancy, labor or at the time of the repeat operation.

2. At The Mount Sinai Hospital the repeat cesarean section is slightly more frequent than the primary operation, a reversal of the situation seven years ago when the obstetrical series was only three years old.

3. No maternal death occurred in the 1028 patients having a repeat cesarean section.

4. The uncorrected perinatal mortality in repeat section (including all fetuses weighing 400 Gm or more) was 29 (2.8%).

5. In the emergency repeat sections the uncorrected fetal loss was 15 (40.5%) and in the elective repeat sections the uncorrected fetal loss was 14 (1.4%).

6. Nine per cent of the infants weighed less than 2500 Gm, with an incidence of 83.8 per cent in the emergency repeat sections and an incidence of 6.2 per cent in the elective repeat sections.

7. Spinal anesthesia, unless otherwise contraindicated, was the anesthetic chosen.

8. Prematurity was no serious problem in the uncomplicated elective repeat section group. Of 62 premature infants, only 4 weighing less than 2500 Gm died.

9. Hyaline membrane disease accounted for the death of two infants, one in the emergency and one in the elective repeat section group.

10. Eight of the 29 infants lost at repeat section died because of congenital abnormalities. All were in the elective repeat section group, a high incidence, perhaps a sampling error.

11. There were 23 post-cesarean scar ruptures or dehiscences in the 1028 repeat sections, an incidence of 2.2 per cent.

12. Twenty-one scar ruptures occurred in previous low segment operations

and two in previous classical scars. One classical scar rupture was catastrophic in nature, the other silent.

13. Two infant deaths were associated with scar rupture at repeat section. One was definitely due to the rupture (classical). The other weighed only 600 Gm, occurring in an emergency repeat section for marked bleeding from a placenta previa at 26 weeks' gestation.

14. Sixteen uterii with scar separation were repaired and seven were removed.

15. The earliest rupture of a post-cesarean scar, found at 26 weeks of gestation, was observed in the course of surgery for placenta previa.

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Diaphragmatic Hernia through the Foramen of Morgagni

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Morgagni hernia is the least common variety of diaphragmatic hernia. While more than one hundred cases have been reported and the true incidence is undoubtedly considerably greater, they are rare in any one individual's experience. Before roentgenography, the identification of such hernias was usually accidentally made by the pathologist. However, even with roentgenographic assistance the diagnosis is often missed, particularly when the hernial sac contains omentum alone. To illustrate, in 1951 Saltzstein (1), Linkner and Scheinberg collected 44 cases from the literature and added one of their own. Twenty-one of the cases were operated upon. Of these, the preoperative diagnosis was correct in eleven only. In 1956, Betts reported five cases (2). In but two of these did the case reports indicate that the correct diagnosis had been made preoperatively. In the series of Boyd and Wooldridge in 1957, nine such hernias in eight patients were reported (3). The diagnosis was definitely made before operation in just four. Of the remaining five, the diagnosis was mediastinal tumor in three, and both pleural cyst and Morgagni hernia were considered in two.

Operative correction of Morgagni herniae is desirable and for reasons which will be stated later, the abdominal route is highly preferable. Since the alternate diagnosis of some variety of thoracic or mediastinal tumor necessitates a thoracic approach, diagnostic precision is more than an academic nicety. It is with this in mind that the subject is reviewed and the following three cases are presented.

CASE REPORTS

Case 1. A 56 year old man was admitted on December 26, 1954 with a history of the gradual onset of vomiting about four months prior to administration. This was associated with a feeling of substernal tightness, and shortly thereafter cough supervened. All symptoms were progressive. The vomiting increased, and while at first it could be corrected by sitting up after meals, subsequently even this was not sufficient to keep it in abeyance. The vomiting at first was for solid foods; later, even liquids were often vomited and food ingested the previous day would be brought up. The cough increased in severity and became intractable. Fourteen pounds in weight were lost. The patient was x-rayed prior to admission and was told he had an "upside-down stomach." Examination on admission showed some evidence of weight loss. Questionable bowel sounds were heard at the base of the right chest. Apart from this, there were no positive physical findings. The upper gastrointestinal series was repeated, showing a herniation of the entire distal half of the stomach and a loop of bowel resembling colon into the anteromedial right chest. The herniation took place through a wide anterior opening just to the right of the midline. The films were particularly interesting in that they actually outlined the site of passage of the stomach from the abdomen into the chest (Figs. 1, 2). The diagnosis of herniation through the right foramen of Morgagni was quite clear.

The hernia was repaired without difficulty through an abdominal approach. A right upper

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rectus muscle splitting incision was made. The sac contained stomach, transverse colon and omentum. These were readily reduced and the sac, which extended up to the level of the 3rd costal cartilage, was pulled down into the peritoneal cavity, a suture ligature taken through its neck, and the excess cut away. The defect in the diaphragm was elliptical, the long axis parallel to the costal margin. It measured about 2½ by 1¼ inches. It was closed

Fig. 1. Case 1. Distal half of stomach in right chest. Site of passage into chest seen to be just to right of midline.

with two layers of interrupted silk sutures, the first closing the orifice transversely and the second overlapping additional diaphragm over the suture line and fixing it to the inner surface of the costal margin. The postoperative course was entirely uneventful. All symptoms disappeared postoperatively. The last follow-up was June 19, 1962 at which time the patient was still asymptomatic.

Case 2. A 65 year old woman was admitted on March 22, 1955 with complaints of postprandial nausea, regurgitation and vomiting, constipation, angina, dyspnea, and palpitation. The symptoms had been present for more than ten years. She was known to have had a diaphragmatic hernia since 1937 and there was a long-standing history of arteriosclerotic

heart disease. In 1940 a supravaginal hysterectomy had been performed for fibroids and, at this operation the presence of a diaphragmatic hernia was verified although it was thought by the surgeon that the defect in the diaphragm was in the region of the right dome and that it was the small intestine that was herniated into the chest. In 1942, the patient had a right thoracotomy with excision of a tumor of the right lower lobe. The tumor proved to be a tuberculoma. The diaphragmatic hernia was again seen and was observed to enter through

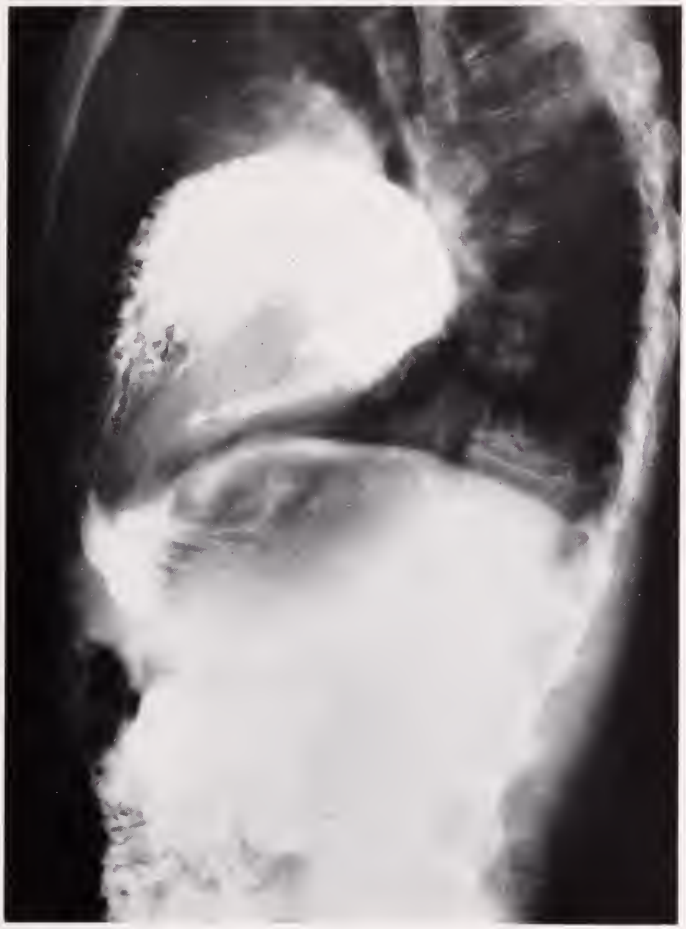

FIG. 2. Case 1. Lateral view showing anterior position of passageway into chest.

the foramen of Morgagni. According to the surgeon, it contained large bowel, but no attempt was made to repair it. X-rays in 1943 verified the presence of a right diaphragmatic hernia containing stomach, duodenum and hepatic flexure of the colon, probably incarcerated within the sac. Figures 3 and 4 show the hernia with and without barium. From that time to the present admission there was an increase in the severity of the symptoms referable to the herniated bowel. Because of the cardiac status, severe emotional difficulties, and resistance on the part of the patient, there had been great reluctance to insist upon surgery, but the persistence of symptoms and the possibility of incarceration finally left no alternative. It was also realized that some of the symptomatology attributed to the heart might prove to be due to the hernia.

Repeat x-rays showed a persistence of the hernia and the patient finally consented to admission for surgical repair. The lesion was approached abdominally through a right upper paramedian incision. A right transverse elliptical subcostosternal defect, easily admitting three fingers, was found. The hernial contents consisted of hepatic flexure, most of transverse colon, stomach, pylorus and duodenum. All these were easily reduced. The sac itself could not be readily reduced and accordingly was left in situ. The falciform ligament, which entered the sac, was divided. The defect in the diaphragm was repaired by approximating its anterior to its posterior edge with interrupted silk sutures, reinforcing this by

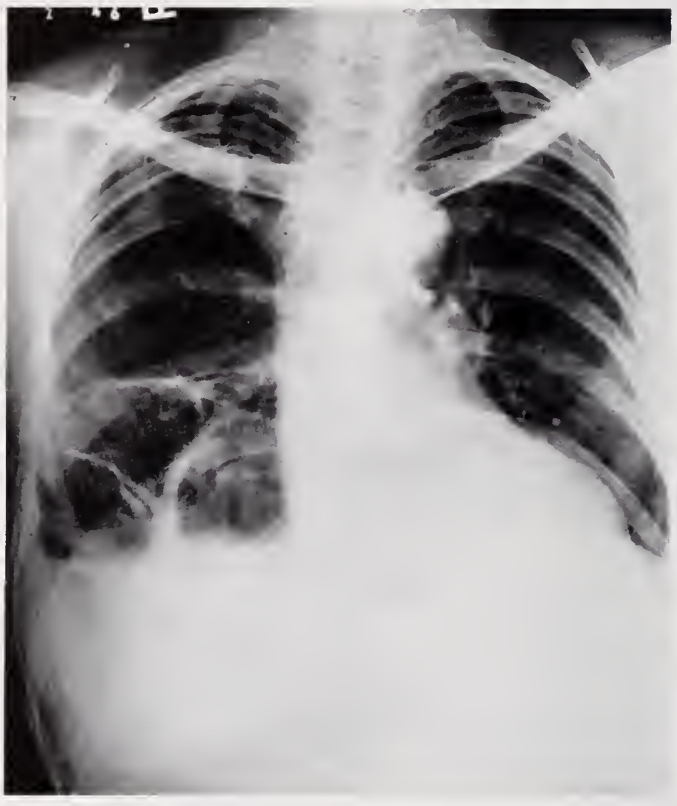

Fig. 3. Case 2. Plain chest film showing gas-filled shadow in right lower chest.

a second layer which brought the diaphragm behind the suture line to the costal margin. The sac was emptied of air by a catheter attached to underwater drainage. The anesthetist exerted positive pressure on the lungs and the catheter was removed just prior to complete closure of the defect. The postoperative course was uneventful and the patient was discharged from the hospital on April 13, 1955. Almost all symptoms disappeared following surgery, and as of September, 1962, the only complaint was of slight occasional angina.

Case 3. A 58 year old man was admitted on September 18, 1956 for care of a "chest lesion" that had been accidentally discovered by routine chest x-ray. The patient was entirely asymptomatic. He had been told that he had a lung tumor. Plain film of the chest (Figs. 5, 6) showed a large, circumscribed, ovoid, soft tissue density in the anteromedial aspect of the right lower lung field contiguous with the anteroinferior mediastinum and extending down to the diaphragm. The margins of the shadow were sharply circumscribed. Its opacity was somewhat

less than would be expected for the ordinary variety of chest tumor or fluid-containing lesion. It was distinctly less dense than the heart shadow. This radiolucency was compatible with a benign soft tissue mass of fatty composition. Lipoma was therefore to be considered and omental herniation through the diaphragm ruled out although some observers thought the shadow suggested a cyst or even a loculated effusion. A barium enema was done, demonstrating a sharp upward angulation of the mid-transverse colon. The transverse colon was

Fig. 4. Case 2. With barium, shadow shown to be stomach and colon.

higher than usual and the apex of angulation was at the upper limit of the abdomen (Fig. 7). In the lateral view this angulated portion was seen to lie far anterior in position (Fig. 8). The films, it was felt, gave quite conclusive evidence of omental herniation through the foramen of Morgagni.

The hernia was repaired through a right upper rectus muscle splitting abdominal incision. The findings were what had been anticipated, namely, the greater omentum was not visible, having herniated through a right foramen of Morgagni defect. The transverse colon was pulled upward and forward by the herniation. The omentum could be delivered without difficulty through the diaphragmatic defect which measured about 2¾″ in its transverse diameter and about ¾″ from front to back. The peritoneal sac was delivered from the chest,

transfixed, and amputated. The diaphragmatic defect was closed from front to back with two layers of interrupted silk sutures, the second layer fixing the diaphragm behind the defect to the anterior chest wall. The postoperative course was entirely uneventful. Figure 9 is a postoperative chest film showing absence of the chest mass. The patient, last seen in August, 1962, has remained well.

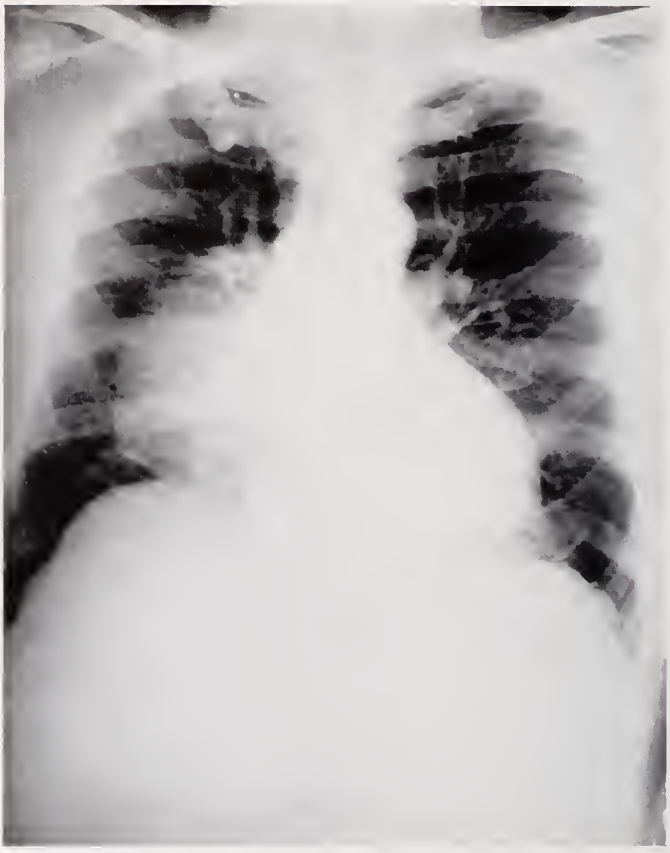

Fig. 5. Case 3. Circumscribed, ovoid, soft tissue density in medial aspect of right lower lung field. Note density of shadow less than that of heart.

DISCUSSION

Hernias through the foramen of Morgagni or space of Larrey have variously been called subcostosternal, retrosternal, parasternal or anterior diaphragmatic hernias. The foramina of Morgagni are triangular spaces on either side of the midline sternal slip of diaphragm. The base of the triangular is anterior. Occasionally the sternal attachment of the diaphragm may be absent. The two spaces may then be fused into one large one. They are weak areas, devoid of muscle and traversed by the superior epigastric vessels. Pleura covers the thoracic aspect, peritoneum the abdominal, with areolar and connective tissue between. The left side is reinforced by the pericardial attachments. Probably for the

latter reason herniation is much more common through the right space although both left sided and bilateral Morgagni hernias do occur (3, 8).

Foramen of Morgagni hernias always have a sac. The only other diaphragmatic hernia in which this is also the case is hiatus hernia. The round and falci-

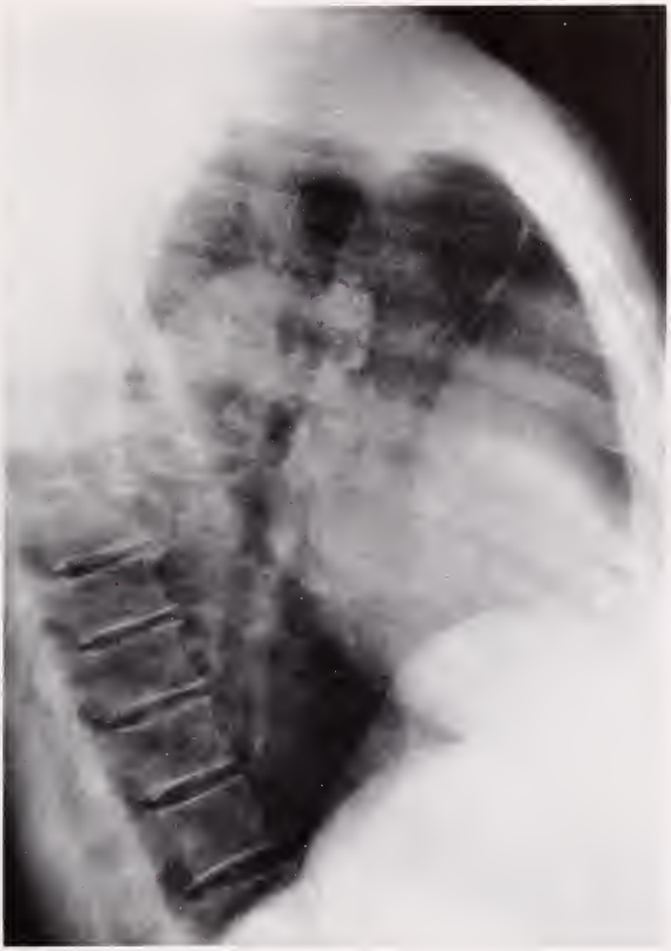

FIG. 6. Case 3. Lateral view showing anterior position of lesion.

form ligaments are almost invariably involved in the sac. The presence of a sac indicates formation of the hernia after the peritoneal cavity has been closed off from the pleural. Whether this type of hernia is congenital or acquired is controversial. Harrington gives an excellent summation of the arguments, concluding that the lesions are essentially direct hernias which, though they appear usually in later life, do so through a congenital defect in the structure of the diaphragm or a faulty attachment of the diaphragm to the sternum or costal cartilages (5).

The clinical picture is highly variable and is dependent upon the abdominal structures involved, the presence of obstructive phenomena, and the degree of impingement upon thoracic structures. Thus, there may be no symptoms, or mild or severe complaints may be referable to the gastrointestinal, respiratory or cardiovascular systems. The patient may complain of "stomach trouble," *i.e.*, in-

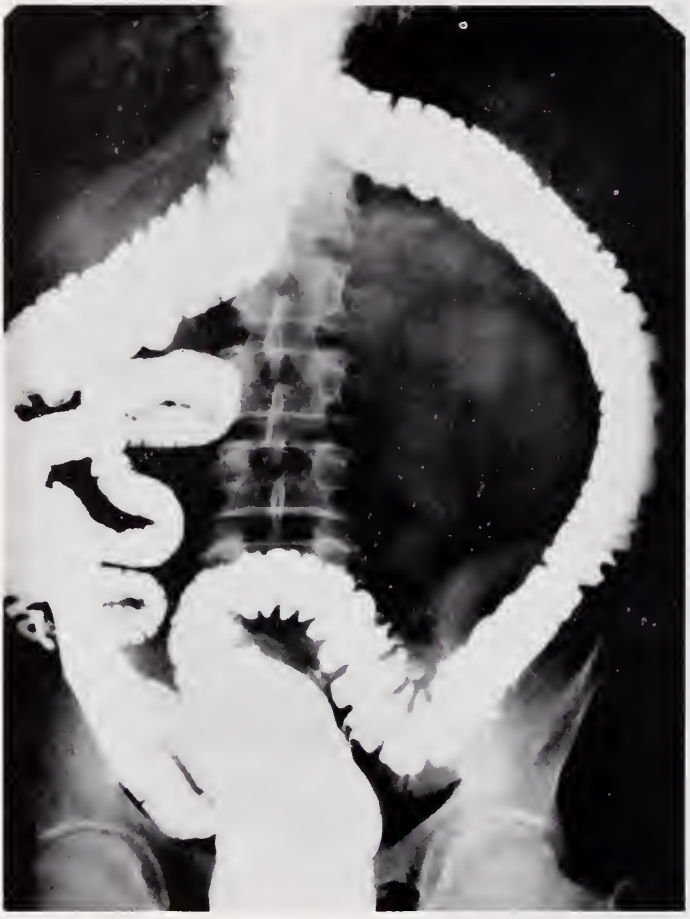

FIG. 7. Case 3. Barium enema showing sharp upward angulation of colon, apex, angulation at upper limit of abdomen.

digestion, pain, postprandial distress, swallowing difficulty, fullness, constipation, gurgling in the chest, or attacks of partial intestinal obstruction with pain, distention, nausea and constipation. Or, there may be cough, dyspnea, chest pain, smothering sensation on lying down, husky voice, or palpitation. Obstructive symptoms are more common in later life when increasing fat deposits in the omentum and mesentery sometimes occur (6).

Physical signs are usually noncontributory or at best non-specific. Rales, or rhonchi may be present. There may be dullness or tympani on percussion and

the apex beat may be shifted. A succussion sound coinciding with the heart beat is said to be pathognomonic (7). A deformity in which the lower sternum projected forward beyond the ribs and costal cartilages was observed in two

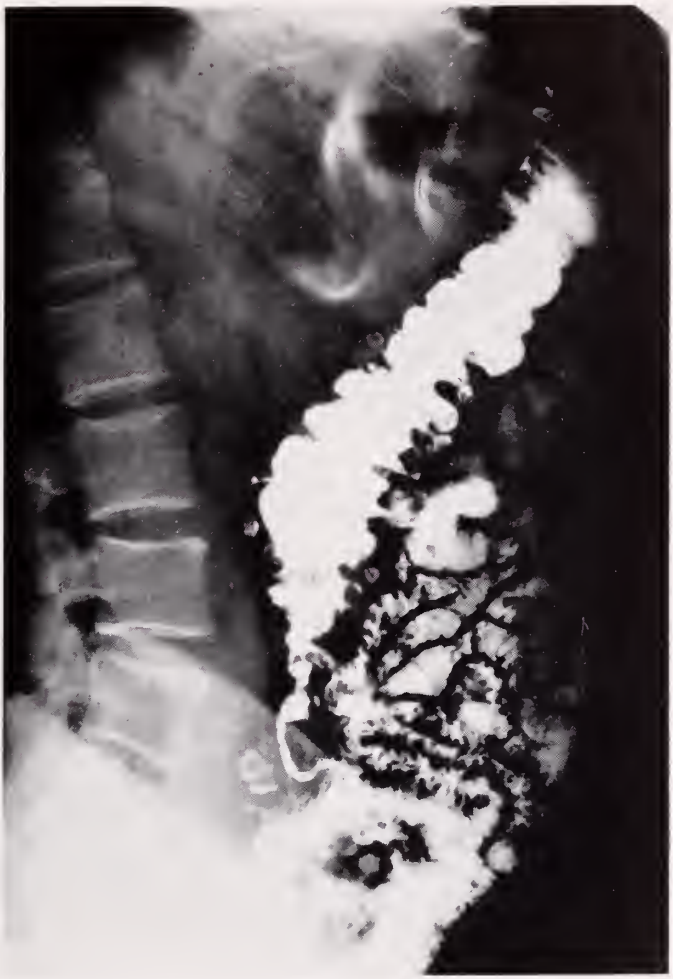

FIG. 8. Case 3. Lateral view showing anterior location of apex of angulation.

cases by Bingham (6). In both these cases, one an infant and one a child, the diaphragmatic defect was in the midline and the sternal attachment was absent.

It is the x-ray that is all-important diagnostically. The plain film shows a rounded soft tissue density in the lower anterior midportion of the pulmonary field at the cardiophrenic angle. Except for its mesial border which cannot usually be separated from the heart, its borders are as a rule well defined. The pleura may be seen reflecting from the mass to the chest wall indicating an extrapleural location (2). A gas shadow may be present within the mass. Should this be ar-

ranged in a typical intestinal pattern it is diagnostic, but unfortunately this is not always the case. When omentum alone has herniated, the only diagnostic lead from the plain film is that the mass has a translucency or diminished density suggestive of fat. In such a case the lateral film of the upper abdomen may show the unusually high and anterior position of the transverse colon outlined by the gas in it.

When stomach, small bowel or colon is contained in the sac, barium studies outline it in the characteristic anterior mediastinal position. It may even

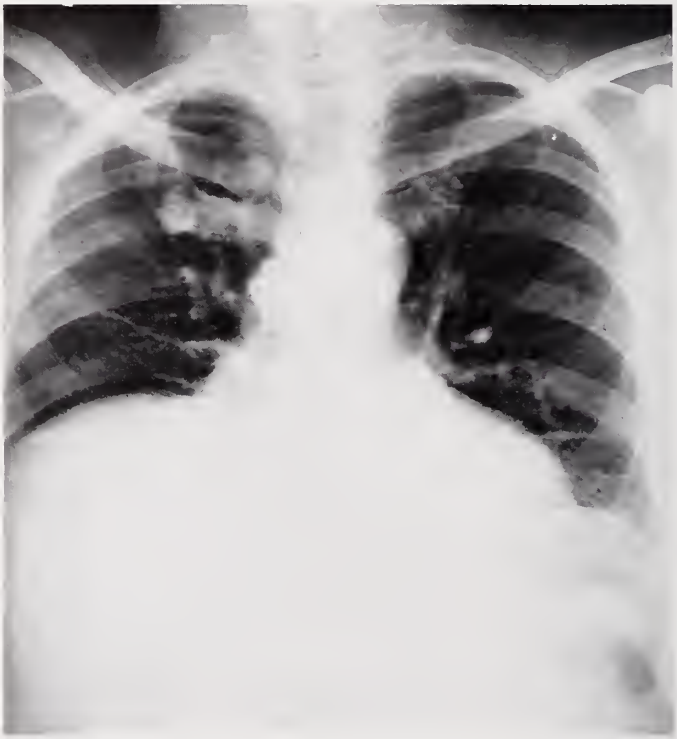

Fig. 9. Case 3. Postoperative film showing absence of chest mass.

be possible to demonstrate the site of passage through the diaphragm as in Figures 1 and 2. If omentum only is present in the sac, barium may show upward anterior displacement of the colon with increased angulation as in Figures 7 and 8. With alternate inspiration and expiration, alternate widening and narrowing of the angulation of the colon may be seen. Finally, pneumoperitoneum may be helpful in establishing a diagnosis.

If the condition is thought of, and appropriate roentgenographic studies are employed, diagnosis should offer no difficulty. Nevertheless, it apparently often has. Differential diagnosis must be made from any pathologic process that can cast a shadow in the anterior and midportion of the pulmonary field at the cardiophrenic angle, including not only mediastinal tumors such as lymphoma,

lipoma, thymoma, teratoma and peripheral pulmonary neoplasms, but also pleural, pericardial, hydatid and bronchial cysts. A localized pleural collection, or pleural thickening may be simulated and occasionally eventration of the diaphragm may even be suggested. Proper interpretation of the plain x-rays should at least suggest Morgagni hernia; ordinarily barium studies should then establish the diagnosis. The greatest diagnostic difficulty arises when omentum alone is contained in the sac.

Surgical repair is advisable because 1) of associated symptoms, 2) of the danger of incarceration, obstruction or strangulation, or 3) a preoperative diagnosis has not been made. There is general agreement that the abdominal approach through an upper right rectus or midline epigastric incision is much to be preferred. The hernial contents are reduced more safely and easily and the opening in the diaphragm is much more accessible via the abdomen, making satisfactory closure of the defect easier. Moreover, if the hernia should by chance traverse the left Morgagni foramen, or should the defect be bilateral or associated with hiatus hernia (7, 8), both sides or both herniae can be reached through the abdominal approach. In the rare instance, in which broad adhesion of the contents of the sac prevents their reduction by traction, it is easy enough to extend the incision into the chest although I know of no case in which it has been necessary to do so. By way of contrast, in many instances reduction of the contents of a Morgagni hernia has been impossible through the thoracic approach and repair of the defect may be awkward (8). By and large, in these cases, a transthoracic route was used because of a preoperative diagnosis of mediastinal or intrathoracic tumor and, of course, when a definite diagnosis cannot be established it is still advisable to approach the lesion via the thorax. To illustrate the technical difficulties encountered transthoracically, of the first four cases reported by Harrington (6), the thoracic approach was used in one because of diagnostic difficulties. It proved to be impossible to reduce the hernial contents, an enormous omental fat apron, by this route. Repair was effected later without difficulty by the abdominal route. In 1956, Betts reported five cases (2). One case was associated with tuberculosis of the right upper lobe. A right upper lobectomy and thoracoplasty were done; the hernia was observed but not treated. The other four were also approached by thoracotomy. In only one could the contents be reduced. In two, the contents consisted of omentum which had to be resected, while in the last, which contained colon, it was necessary to extend the incision across the costal margin into the right rectus region in order to reduce the contents and repair the hernia.

Following reduction of the contents, an attempt should be made to ablate the sac. If any difficulty is encountered in doing so there should be no hesitancy in leaving it in situ. In such cases, Harrington (5) recommends dividing the round ligament so there is no tendency to drag the liver up. He also suggests making several incisions through the peritoneum of the wall of the sac to prevent accumulation of fluid after the neck has been closed. The defect is usually a transverse ellipse offering no difficulty in closure. If possible the edges are overlapped. The falciform and round ligaments may be used to bolster the re-

pair. Silk was a perfectly satisfactory suture material in the three cases reported above although Harrington recommends living fascia lata (5). Harrington also suggests that large transverse openings extending beneath the sternum may be closed best by suturing the posterior margin of the defect to the posterior rectus sheath and the anterior thoracic wall (5). He protects the closure by temporary phrenic paralysis. We did not find it necessary to employ phrenic crush in any of our cases, but in all, the second layer of repair brought the diaphragm behind the closed defect to the anterior chest wall in front. In most instances, the repair should be simple technically when approached from below the diaphragm. The recurrence rate should be negligible.

SUMMARY

1. Hernia of the foramen of Morgagni is discussed.
2. The importance of preoperative diagnosis is stressed.
3. Repair via the abdominal approach is described.
4. Three cases are added to the literature.

ACKNOWLEDGMENT

Case No. 3 is presented through the courtesy of Dr. David N. Roginsky.

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Essential Hematuria and Retroperitoneal Cyst

A Case Report

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INTRODUCTION

So-called essential hematuria is not an uncommon urological condition. Such a case, herewith presented, was a rather serious diagnostic problem.

CASE REPORT

A 26 year old Negro female, was perfectly well until four weeks prior to admission to the hospital. At that time, she had an episode of total, painless persistent hematuria, associated with burning at the end of micturition and an unpleasant odor to the urine. Additional complaints were a heavy feeling on the right side of the abdomen accentuated when lying down, and moderate constipation. There were no other symptoms. The past history was noncontributory except for an episode of anemia three years prior to admission which was treated successfully on an ambulatory basis.

Physical examination showed a healthy, well-nourished woman in no acute distress. The patient was afebrile and remained so during the entire hospital stay. The physical findings were completely negative except for the presence of a large, oval mass occupying the lateral half of the right midquadrant of the abdomen. This mass was deeply situated, firm, smooth and very tender, well delimited and of hard elastic consistency. Liver, spleen and kidneys were not palpable.

The patient continued to have total hematuria which stopped only two days prior to her discharge from the hospital.

LABORATORY DATA

1. Urine analysis
   - Albumin: 2 plus
   - Urine loaded with RBC's, occasional WBC's
   - Urine culture: negative
   - Urine culture and smear for acid fast bacteria: negative
2. Complete blood count

Hemoglobin	11.5 Gm/100 ml
RBC	4,800,000/cu mm
HCT	35 per cent
WBC	8,900/cu mm Normal differential
Platelets	270,000/cu mm
ESR	6 mm/hour

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3. Chemistries
   BUN 7 mg/100 ml
   Uric acid 3.4 mg/100 ml
   All other chemistries: normal
   Wasserman: negative
   Cephalin flocculation: negative
4. Hematology
   Sickle cell preparation: no sickling observed on three occasions
   Bleeding time, clotting time, clot retraction, serum prothrombin time: all normal
   No fibrinolysis
   Rumpel-Leed's test: negative
   Electrophoresis: hemoglobin A 100 per cent
5. X-rays
   Chest x-rays: normal
   Gall bladder series: normal
   Intravenous pyelogram: (Fig. 1) shows good function bilaterally, the kidneys are normal in size, shape and location. The ureters and bladder appear to be normal. On all the films, there is an oval mass in the right midquadrant which seems to be independent of the right kidney.
   Presacral pneumogram (Fig. 2) showed the previously described mass to be completely separated from the right kidney.
   Barium enema (Fig. 3): the previously described mass was displacing the ascending colon medially and anteriorly. There was no intrinsic pathology of the large bowel.
   Right retrograde pyelogram (Fig. 4): the kidney is normal in size, shape and architecture. The calyceal system is normal and does not present any filling defects.
   The ureter is normal throughout its entire course.

HOSPITAL COURSE

The patient was cystoscoped and on three different occasions blood was seen emerging from the right ureteral orifice. The trigone was slightly injected but otherwise, cystoscopy was unrevealing. A PPD test was positive. The urine was negative for acid fast bacteria on culture and on smear. A complete hematological study was negative. There was no coagulation defect and no hemoglobinopathy.

With continued bleeding, a mass in the right middle quadrant, and with the other findings, the most probable diagnosis was a retroperitoneal neoplasm. This warranted a surgical exploration.

Through a right paramedian transperitoneal incision, exploration disclosed an oval cyst, approximately the size of a large orange, lying immediately adjacent, but completely separated from the ascending colon. The cyst was freed and enucleated and removed intact. It contained clear fluid and proved to have a fibrous wall and mesothelial lining. In addition, some tall mucus-producing cells were seen.

The patient made an uneventful convalescence, but continued to have hematuria, which ceased spontaneously only two days prior to her discharge.

Pathology report showed a fibrous cyst wall with mesothelial lining and mucus-producing cells (peritoneal cyst, inclusion type).

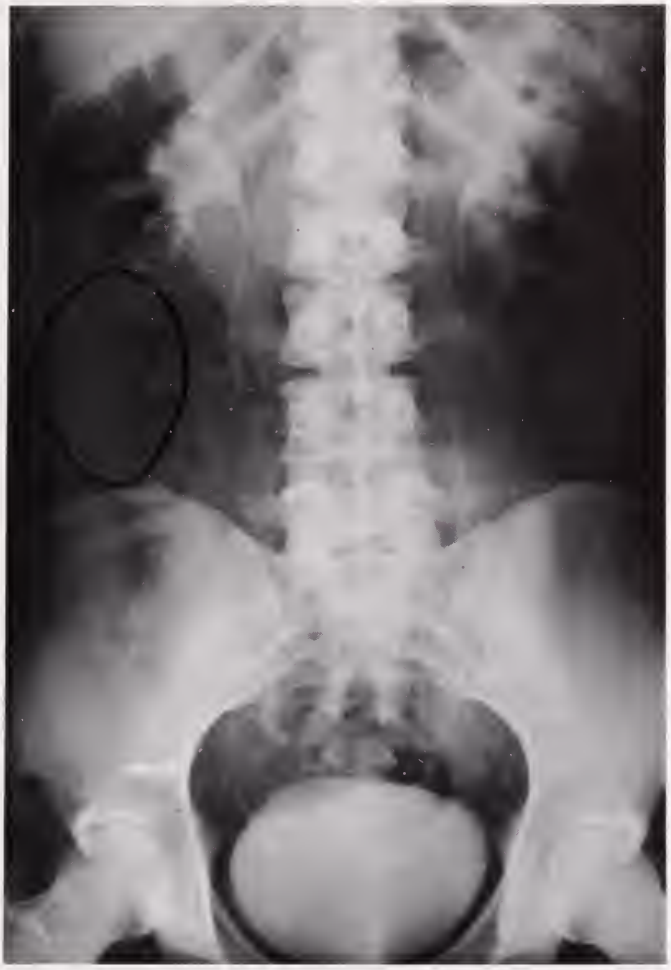

FIG. 1. Intravenous pyelogram.

DISCUSSION

In view of the completely negative urological examination, including retrograde pyelogram and retrorectal air insufflation, a negative urine culture and negative acid fast bacteria studies and the absence of any blood pathology, this patient has to be considered in the category of essential hematuria. We agree that this term is unsatisfactory. However, from time to time, there are cases of hematuria occurring in otherwise healthy people in whom no detectable cause for the hematuria can be found. Some of these patients have undergone nephrec-

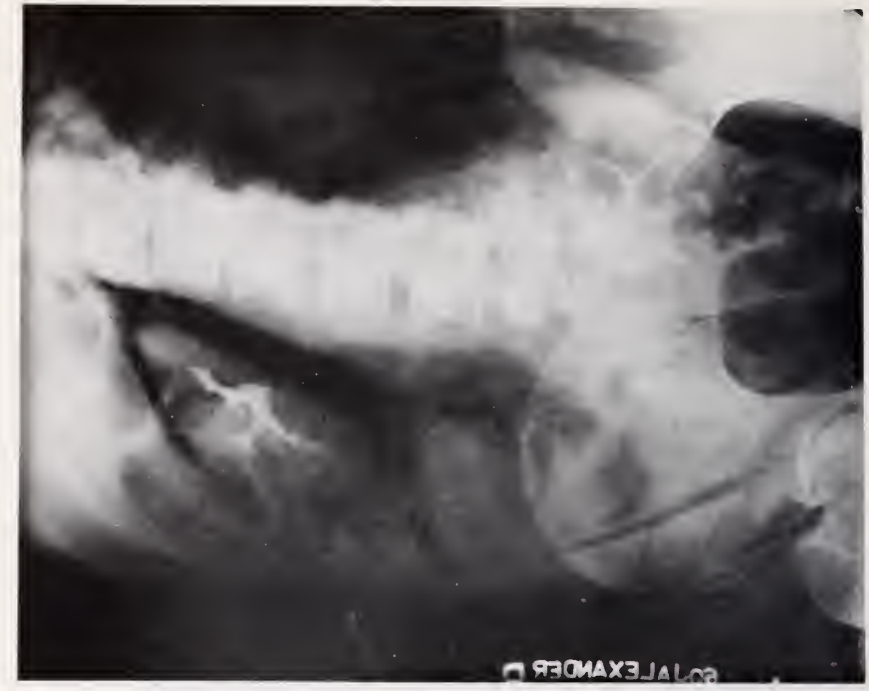

Fig. 2B. Presacral pneumogram.

Fig. 2A. Presacral pneumogram.

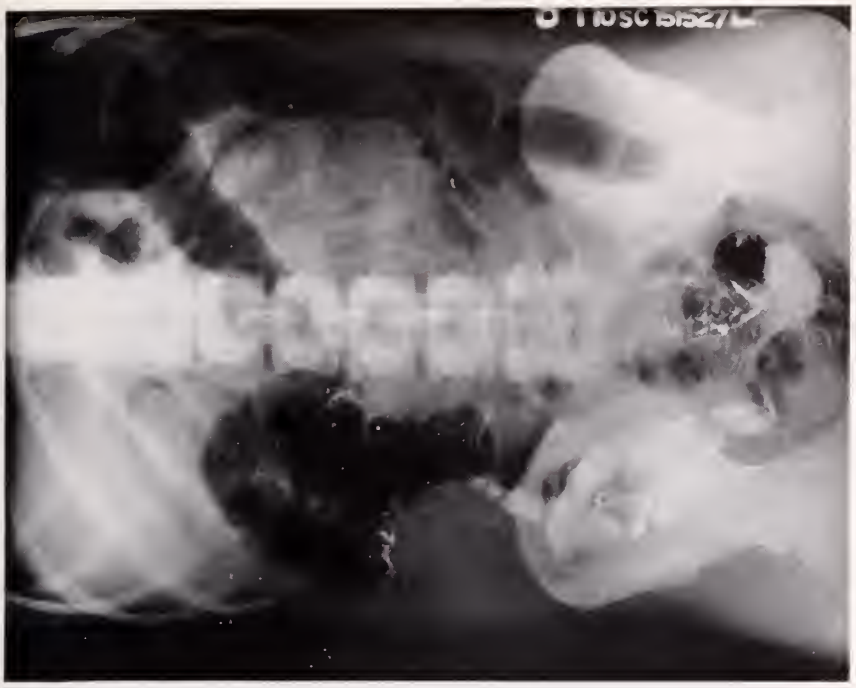

Fig. 3B. Barium enema.

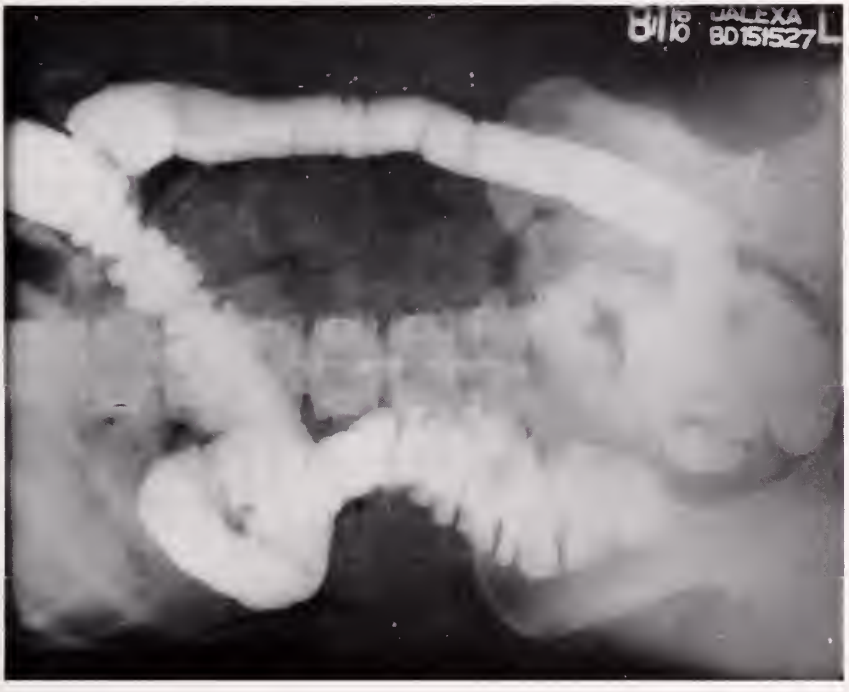

Fig. 3A. Barium enema.

tomy for prolonged bleeding but serial sections of the kidneys failed to show any pathology. Many authors refer to essential hematuria as renal epistaxis (1, 2).

The classification of this patient's cyst presented a serious difficulty. According to Campbell, there is an entire category of retroperitoneal cysts comprised in the group of perirenal cysts. The true perirenal cysts are retroperitoneal (3, 4). The acquired perirenal cysts (due to extravasation, malabsorbed hematomas)

FIG. 4A. Right retrograde pyelogram.

are not actually retroperitoneal. The true perirenal cysts are retroperitoneal because they are derived from the Wolffian and Mullerian ducts and lymphatic system. Wolffian duct cysts are cystic dilatations of the ureter or remnants of pronephric, mesonephric or metanephric structures. Mullerian duct cysts are found in children and adults alike and are always situated at the midline where they may produce bowel obstruction and bladder-neck compression (5). Lymphatic cysts are usually connected with chyle ducts. Another group of cysts are mesenteric cysts, which are usually found in the leaves of the mesentery or at its root and are lined with mesothelium. Dermoid cysts which can be retroperitoneal contain squamous epithelium.

In Pack and Ariel's series which had a total of 120 retroperitoneal tumors, 103

(85.8%) were diagnosed as malignant (6). The most common benign retroperitoneal tumors were the epithelial cysts. The most frequent retroperitoneal tumors, both benign and malignant, are of mesodermal origin (68.3%). Cysts of the retroperitoneum were rare. Handfield-Jones defined the retroperitoneal cysts as those cysts lying in the retroperitoneal fatty tissues which have no con-

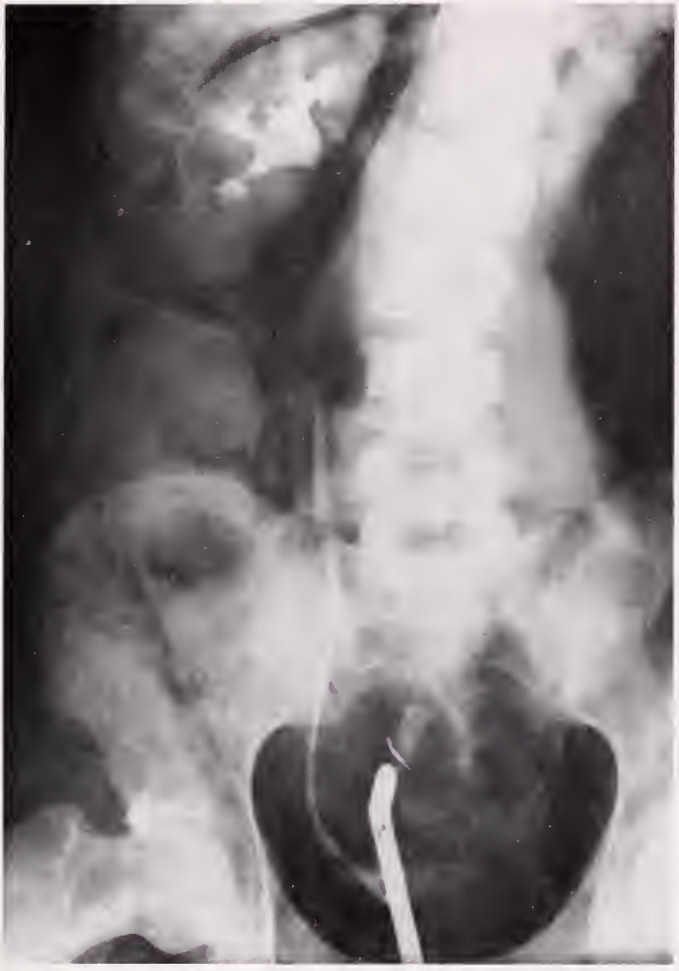

FIG. 4B. Right retrograde pyelogram.

nection with any adult anatomical structure save by areolar tissue (7). According to a modified classification of the one given by Handfield-Jones, the cysts of the retroperitoneal space can be considered as: 1) cysts of urogenital origin, 2) cysts of mesocolic origin, 3) teratomatous and dermoid cysts, 4) lymphatic (or chylous cysts).

Cysts of urogenital origin are found near the kidney or behind the colon near the pancreas. They are most frequent in patients between the ages of 15 and 50, more often on the left side of the abdomen, and predominately in females.

An absolute criterion delineating a cyst as of urogenital origin is the presence of primitive glomeruli or renal tubules in the cyst wall. The wall is thin, fibrous, covered by epithelium, which is usually of the low columnar type but which may also be flattened, especially if the fluid contained in the cyst is under pressure. The cyst contains either clear or brown fluid. This type of cyst is usually very easily enucleated. This group of cysts corresponds to the perirenal cysts of Wolffian and Mullerian origin in Campbell's study.

Similar to the urogenital cysts are the cysts of mesocolic origin but they differ in location and in manner of origin. They originate in the area between the ascending, transverse and descending colon. They originate from imperfect fusion of the peritoneal layers. The teratomas are congenital tumors composed of multiple tissues. Dermoid cysts are highly differentiated teratomas consisting of mature adult tissue, which may contain components of the ectoderm, endoderm and mesoderm. The lymphatic or chylous cysts are found in the retroperitoneal space or leaves of the mesentery and they contain white or yellow, thick fluid composed of fatty globules. Cysts which are not really retroperitoneal are the enterogenous cysts (in the layers of the intestinal wall, intestinal duplication, cysts arising from Meckel's diverticulum).

This patient's cyst could not be definitely classified in any of the above categories. The mucus-producing cells are normally found in the alimentary and genital tracts.

On the basis of our present knowledge, we decided to consider this as a benign inclusion type cyst of the peritoneum. This patient was discharged after four weeks of hospitalization and is followed regularly in the Out-patient Department. At the present time, she is completely asymptomatic.

SUMMARY

A case of essential hematuria associated with retroperitoneal cyst is presented.

The term, essential hematuria, is discussed and defined.

A review of retroperitoneal cyst and neoplasm is briefly outlined.

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Sytemic and Local Conditions Predisposing to Ischemic and Occlusive Cerebrovascular Disease

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Cerebral angiography has produced a revolution for the diagnosis and management of the patient with a "stroke," and it is no longer possible to be a student of cerebrovascular diseases without a practical knowledge of the technique (1). As in all revolutions, however, not all of the changes brought about by the increased use of angiography have been desirable. Perhaps the least desirable effect of routine angiographic study of patients with ischemic brain disease, has been the tendency of some physicians to forget that a cerebrovascular accident may be the initial manifestation of unrecognized systemic disease. All too often today, the neurologist caring for a patient with a "stroke" is more concerned with obtaining "time" for angiography in the Radiology Department, than with the results of preliminary blood, urine, electrocardiographic and other tests.

From August 1962 through March 1963, 120 patients were hospitalized* because of occlusive or ischemic cerebrovascular disease. The purposes of this communication are to report the incidence and nature of possible predisposing diseases in 100 of these patients and to review the systemic and local conditions which may contribute to cerebrovascular insufficiency.

MATERIALS AND METHODS

The patients reported are part of a cerebrovascular disease study now underway at The Mount Sinai and Greenpoint Hospitals. For inclusion in this study, all patients must satisfy one of the following criteria: 1) An acute onset of focal cerebral or brain stem symptoms or signs (other than seizures), 2) typical transient focal cerebral or brain stem ischemic attacks, and 3) an arteriographic demonstration of occlusion of a major artery. The 100 patients reported here are essentially consecutive in the study, and represent the first 100 patients with completed hospitalizations. Eighty-four patients were admitted to both the ward and private pavilions of Mount Sinai Hospital, and 16 others were seen initially at Greenpoint Hospital. Sixty-one of these patients were men and 39 were women. Three patients were under 40 years of age, 30 were from 40 to 60, 37 were from 60 to 70, 24 were from 70 to 80, and 6 were over 80 years old. The major cerebral ischemia, or infarction was felt to be in the distribution of a carotid or middle cerebral artery in 85 patients, while the vertebral-basilar system was predominately involved in 15 patients. Seventy-six patients had an abrupt onset of their illness, with maximum deficit at onset. Seventeen patients initially had typical transient ischemic attacks without persistent deficits, and

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seven others had deficits of acute onset which progressed. These patients were investigated with 125 cerebral arteriograms. The results of these studies and the relation of systemic disease to the arteriographic findings, prognosis, and so forth will be presented elsewhere.

For purposes of detecting systemic illnesses, an attempt was made to obtain the following in every patient: complete blood count; hematocrit; erythrocyte sedimentation rate; urinalysis; fasting or two hour post-prandial blood sugar; blood urea nitrogen; cholesterol; electrocardiogram; chest roentgenogram; blood and spinal fluid serology, and hemoglobin electrophoresis in Negro patients. Blood pressure was determined in each arm, and again following a sudden change from the supine to the erect position. All available roentgenograms of the chest, skull or neck were inspected for evidence of intravascular calcifications. These studies were combined with the admission history, the findings on general physical examination and other laboratory findings for the analysis of the data obtained.

RESULTS

By the procedures employed, only 12 of the 100 patients were found to be free of predisposing systemic illness. The conditions encountered in this series are summarized in Table I.

Definite evidence of heart disease was found in 41 patients. Twenty-one of these had old myocardial infarctions, which were probably not causally related to the current cerebrovascular disease. In three other patients, however, the infarctions, all clinically silent, were acute. Nine patients were found to be in congestive heart failure and a history of angina pectoris was obtained in 11. Eleven patients were noted to have atrial fibrillation; this condition was unknown to five patients or their physicians prior to hospitalization for ischemic brain disease. Two other patients had many runs of premature ventricular contractions and complete heart block respectively. The first of these latter arrhythmias was previously unknown. Four patients had evidence of rheumatic heart disease, and one of these had evidence of embolization elsewhere than in the cerebral circulation. Non-specific "ST" and "T" wave abnormalities were noted in the electrocardiograms of 26 patients.

Fifty patients were found to be hypertensive (pressures greater than 150/100 on several occasions); hypertension was not known to have been present in seven of these patients prior to the onset of cerebrovascular disease. Hypotensive episodes, related to treatment for hypertension, were suspected in six patients. However, a definite relation to cerebrovascular insufficiency could be proved in none.

Diabetes mellitus (fasting blood sugar greater than 120 mg% or two hour post-prandial sugars greater than 180 mg%) was noted in 32 patients, 12 of whom had no prior knowledge of the condition. A possible hypoglycemic reaction, related to insulin therapy was felt to be implicated in the onset of cerebral symptoms in one patient.

Three patients were noted to have significant orthostatic and/or carotid sinus hypotension. Acute cerebral signs were related to general anesthesia in two

others. Five other patients showed evidence of recent significant blood loss. Systemic hypotension may well have been a possible contributing factor in these patients.

Eighteen patients had blood cholesterol levels greater than 300 mg%, and three had a blood urea nitrogen above 30 mg%. Two patients had hemoglobin values under 9 Gm% and four had hematocrits over 52%. The two patients with

TABLE I

Systemic Conditions in 100 Consecutive Patients with Ischemic Brain Disease

Condition	No. of Patients
Organic heart disease	41
Myocardial infaretion, old	21
Myocardial infaretion, recent	3
Congestive heart failure	9
Rheumatic heart disease	4
Atrial fibrillation	11
Other arrhythmias	2
History of angina	11
Nonspecific EKG changes	26
Hypertension	50
Diabetes	32
Possible hypotension	16
Antihypertensive therapy	6
Blood loss	5
Other	5
Peripheral vascular disease	12
Hypercholesterolemia	18
Uremia	3
Anemia	2
Polycythemia	4
Unequal brachial blood pressures	6
History of lues or positive serology	5
Calcifications in aorta on x-ray	12
Calcifications in carotid on x-ray	8

anemia were both found to be iron deficient. Adequate hematologic study was not performed in the four patients with elevated hematocrits.

Evidence of peripheral arterial disease was noted in 18 patients. Six patients were found to have significant differences between the blood pressures of the arms. The roentgenograms revealed calcifications in the thoracic aortas of twelve patients and calcifications were noted in the carotid arteries of eight patients.

Three patients had a history of treated lues. Two other patients had positive serological tests for syphilis, which were probably biologically false positives.

Unfortunately, some of the abnormalities noted above could not be investigated further.

DISCUSSION

Many other conditions, in addition to those found in this study, may readily contribute to signs and symptoms of ischemic brain disease. Most of these conditions have been summarized in Table II, which is an extension and modifica-

TABLE II

Survey of Miscellaneous Conditions Predisposing to Ischemic Brain Disease

I. Diseases of the cardiovascular system
  A. Associated with diminished cardiac output
    1. Myocardial infarction
    2. Alterations of cardiac rate or rhythm
    3. Congestive heart failure
    4. Miscellaneous
      a. aortic stenosis
      b. intracardiac tumor or thrombus
      c. pulmonary vascular disease
      d. other
  B. Associated with reduction of systemic blood pressure
    1. Reduction of cardiac output
    2. Conditions causing shock
    3. Acute blood loss
    4. Carotid sinus hypersensitivity
    5. Postural hypotension
    6. Antihypertensive therapy
    7. Miscellaneous
      a. surgery
      b. anesthesia
      c. pulmonary embolization
      d. sepsis
      e. post-sympathectomy
      f. other
  C. Associated with sources of systemic emboli
    1. Left auricular thrombus
      a. mitral stenosis
      b. atrial fibrillation
    2. Aortic stenosis
    3. Endocarditis
      a. subacute and acute bacterial
      b. rheumatic
      c. nonbacterial thrombotic
    4. Mural thrombus after myocardial infarction
    5. Tumor, (*e.g.* myxoma of left auricle)
    6. Heart, chest or neck surgery
    7. Paradoxic
    8. Arteriosclerotic plaques of aorta, other large vessels
    9. Subclavian artery thrombosis (*e.g.* from cervical rib)
    10. Thrombophlebitis of pulmonary veins
    11. Primary myocardial disease
    12. Miscellaneous
      a. air
      b. fat
      c. other

TABLE II—*Continued*

- D. Mechanical obstruction of the great and neck vessels
  - 1. Obstruction due to neoplasm
    - a. upper mediastinum
    - b. neck
  - 2. Aortic arch obstruction
    - a. atherosclerosis
    - b. syphilis with or without aneurysm
    - c. nonspecific aortitis
    - d. dissecting aneurysm
    - e. trauma
    - f. systemic disease
  - 3. Obstruction due to osseous structures
    - a. cervical rib
    - b. arch of the atlas
    - c. cervical osteophytes
    - d. congenital cervical spine abnormalities
  - 4. Miscellaneous congenital abnormalities
- E. Hypertension
- F. Congenital cardiac lesions

- II. Diseases of the Hemopoietic System
  - A. Polycythemia
  - B. Anemia
  - C. Hemoglobinopathy
  - D. Thrombotic thrombocytopenic purpura
  - E. Other
    - 1. Thrombocytosis
    - 2. Macroglobulinemia

- III. Toxic-Metabolic States
  - A. Hypoglycemia
  - B. Drugs (*e.g.* barbiturates)
  - C. Fever, hypoxia, etc.
  - D. Diabetes mellitus
  - E. Hypercholestérolemia
  - F. Other

- IV. Systemic Infections
  - A. Mucormycosis
  - B. Syphilis
  - C. Tuberculosis
  - D. Viral
  - E. Pyogenic
  - F. Parasitic

- V. Miscellaneous Systemic Diseases
  - A. Lupus erythematosus
  - B. Temporal arteritis
  - C. Periarteritis nodosa
  - D. Rheumatic fever
  - E. Thrombo-angiitis obliterans
  - F. Other

tion of an outline of cerebrovascular diseases suggested by an ad hoc committee of the National Institute of Neurological Diseases and Blindness (2).

MYOCARDIAL INFARCTION

The association of myocardial infarction with cerebrovascular accidents has been well described in the literature (3–16). Almost all of the authors discussing this association have presented patients in whom the cardiac signs and symp-

TABLE III

Incidences of Cardiovascular Disease in Reported Series of Patients with Cerebrovascular Accidents

Author, Year	Type of Study	Number of Patients	Percentage with			
			Acute Myocardial Infarction	Congestive Failure or Arrhythmia	Source for Emboli	Hypertension
Dozzi (3) 1937	Autopsy	107	11	?	?	?
Dozzi (4) 1939	Clinical	66	12	?	?	?
Hicks and Black (7) 1949	Autopsy	141	?	18	2.1	89
Hicks and Warren (18) 1951	Autopsy	100	5	44	15	?
Wilson, *et al.* (9) 1951	Autopsy	542	10	56	7.4	63
Sturup (10) 1952	Clinical and Autopsy	110	5.8	6.7	?	?
Rogers and Shuman (13) 1954	Clinical	134	14	?	?	?
Cohen (19) 1955	Autopsy	210 (42 acute)	17 (of acute CVA's)	?	1	57
Murray (14) 1957	Clinical	111	18	39	1.4	52
Riishede (20) 1957	Clinical	100	2	10	3	58
Glathe and Achor (15) 1958	Clinical	66	12	?	6	?
Gormsen, *et al.* (21) 1961	Clinical	202	7.5	16	2.5	45
Yates and Hutchinson (22) 1961	Clinical and Autopsy	100	6	6	?	58
Present series 1963	Clinical	100	3	22	4	50

toms were obscured by the more striking cerebral manifestations, as was the case with three patients in the present series. The difficulty of obtaining a history of chest pain in patients who have lost consciousness, or who are aphasic or confused, is stressed, and a plea for routine electrocardiography in patients with acute cerebral insults is made almost universally.

A review of over 1100 published autopsies of patients with myocardial infarction revealed that cerebral infarctions were found in 7.7 per cent (17). As many as 29 per cent of fatal myocardial infarctions may be unrecognized during life because of cerebral manifestations (3). The incidence of acute myocardial infarction in a consecutive series of patients with a diagnosis of "stroke" has been

reported as high as 18 per cent (14). Table III summarizes the frequency of acute myocardial infarction in some published series of patients with cerebrovascular accidents.

There are several possible explanations for the relationship of myocardial infarction to ischemic brain disease. One of these, embolization from a mural thrombus, will be discussed later. Another proposed mechanism, a generalized tendency for intravascular thrombosis due to a hypercoagulable state after myocardial infarction, lacks verification. While the same pathologic process, atherosclerosis, may affect the coronary and cerebral arteries, a recent autopsy study (23) failed to establish a definite correlation between fatal cerebrovascular accidents and the degree of coronary atheromatosis.

The most plausible explanation, however, for the occurrence of focal brain signs at the time of a myocardial infarction may be related to a diminution of cardiac output, reduction of systemic blood pressure, hypoxia, and possibly other factors. It is argued that a pre-existing cerebrovascular occlusion or narrowing becomes clinically significant when the metabolic needs of the area of brain supplied become further compromised by these factors. This is believed to be due to either the failure of existing collateral circulation or the reduction of perfusion pressure through an already narrowed tube.

OTHER CAUSES OF DIMINISHED CARDIAC OUTPUT

Although syncope is a generally accepted manifestation of cerebral ischemia from a variety of cardiac arrhythmias (24), the occurrence of signs of focal brain ischemia in association with disturbances of cardiac rate and rhythm is less readily appreciated. Some of the symptoms of bradycardia initially described by Stokes in 1846 (25), included apoplectic attacks, and a cerebral infarction was found at autopsy in at least one of his patients.

Signs of focal cerebral ischemia have been reported not only with heart block (26), but also with atrial (27) and ventricular (28) tachycardias and atrial fibrillation (29). None of these patients and none of the 13 patients with arrhythmias in the present series, other than those with rheumatic heart disease, were thought to have sustained cerebral embolization. That the effects of arrhythmias are probably related to reduction of cardiac output is suggested by the recent report of diminished carotid blood flow with experimentally induced arrhythmias (29).

Cerebral blood flow has also been shown to be reduced with severe congestive heart failure (30). It is not surprising, therefore, that clinical (31) and pathologic (32) signs of focal cerebral ischemia and infarction in association with severe cardiac decompensation have been reported. The incidences of arrhythmia and congestive failure in some reported series of patients with cerebrovascular accidents are shown in Table III.

Cerebral ischemia, as manifested by syncope, is not uncommon in other conditions (*e.g.* aortic stenosis, intracardiac tumor, pulmonary hypertension) resulting in diminished cardiac output. Although signs of focal brain ischemia do not

occur often with these conditions, at least a theoretical possibility for their occurrence does exist.

SYSTEMIC HYPOTENSION

The association of ischemic brain disease with reduction of systemic blood pressure has been discussed quite often in the recent literature (2, 20–22, 26, 28, 31–35). The occurrence of cerebrovascular accidents in patients with hypotension due to conditions causing shock (22, 31, 34), acute blood loss (22, 28, 35), carotid sinus hypersensitivity (22, 28, 31), postural changes (20, 36), therapy for hypertension (21, 34, 37, 38) and other states (2, 28, 31) is well documented. Signs and symptoms of cerebrovascular insufficiency are reproducible in some patients by reduction of systemic blood pressure below a critical level (20, 26, 39). The frequent occurrence of cerebrovascular accidents at night has been explained by the relative hypotension which occurs during sleep (33, 35). Much experimental evidence for the role of hypotension in the production of ischemic brain disease has also accumulated (28, 31, 40–43).

Systemic hypotension may have been a contributing factor to ischemic brain disease in 16 patients in the present series.

EMBOLIZATION

A definite source for embolization was present in four patients in this series. Emboli from almost any origin may initially manifest themselves in the cerebral circulation. Perhaps the most frequent source for cerebral embolization is a left auricular thrombus, as is most commonly found in patients with rheumatic heart disease. The reported incidence of brain embolism in patients with rheumatic valvular disease varies from 20 per cent (44) to 49 per cent (45). It is commonly believed that atrial fibrillation is the predisposing cause to left auricular thrombus and cerebral embolization (2). Askey (46), however, has suggested that the fibrillation itself may be secondary to mitral stenosis, and it is this latter condition which produces sufficient stasis in the left auricle to allow thrombus formation. Thus, it is not necessary for atrial fibrillation to be present for cerebral embolization to occur in a patient with mitral stenosis. Cerebral emboli can also occur in patients with rheumatic heart disease who have aortic stenosis; the emboli matter in these patients may be particles of calcium derived from the valve itself (47).

The occurrence of cerebral embolization from bacterial endocarditis, both subacute and acute, is well known (48). The incidence of cerebral embolization in subacute bacterial endocarditis, even in the present antibiotic age, is about 12 per cent (49). Emboli from uninfected rheumatic endocarditis have been suggested, but are probably quite rare (32). In recent years there has been increasing recognition of nonbacterial thrombotic (also called "marantic") endocarditis, which is said to be the most common cause for a cerebrovascular accident in patients with cancer (50).

Sometime after a myocardial infarction, mural thrombus formation may allow cerebral embolization. This complication occurred in five per cent of patients with coronary thrombosis in one follow-up study (51). Other possible

causes of cerebral embolization include intracardiac tumor (16, 52), cardiac surgery (53), chest and neck surgery (2), right to left cardiac shunts (54), arteriosclerotic plaques in the aorta (55) and other large vessels (2), and other conditions, which are listed in Table II.

The reported incidence of embolization in some published series of patients with cerebrovascular accidents is shown in Table III.

MECHANICAL OBSTRUCTION OF VESSELS

Cerebral ischemia or infarction as the result of neoplastic compression or of trauma to the great vessels in the mediastinum or neck is possible, although quite rare. Obstruction of an intracranial vessel such as the middle cerebral artery by a brain tumor with resultant infarction, however, has been well documented (19). Intracranial neoplasms may also contribute to distant cerebral ischemia and infarction by their production of tentorial and foraminal herniations which may compress major arteries (56).

Occlusive disease of the aortic arch may readily contribute to cerebral ischemia (16, 57). This so-called aortic arch syndrome may be caused by atherosclerosis, syphilis (with or without aneurysm), trauma, a nonspecific aortitis, and several systemic diseases (57). Dissecting aneurysm of the aorta is another possible cause for great vessel obstruction and signs and symptoms of ischemic brain disease (22, 58). Cerebrovascular accidents can also occur with congenital aortic defects such as coaretation (59), and other extracranial vascular malformations.

Cerebral ischemia and infarction may also be related to vascular compression by osseous structures. Thus, carotid artery thrombosis has been reported in association with cervical ribs (60, 61) and atlantoid compression (62), and vertebral artery compression by cervical osteophytes has been documented (22, 63, 64). Congenital malformations of the cervical spine may also be contributing factors for vertebral artery insufficiency (65).

HYPERTENSION

Although the cerebrovascular complication of hypertension which has received most attention is hemorrhage, cerebral infarction or ischemia is not uncommon in patients with elevated blood pressures (21, 37, 66–69). In a study of 190 patients with malignant hypertension, cerebral ischemia occurred more often than hemorrhage (66). Cerebral infarction was seven times as frequent as cerebral hemorrhage in another study of 103 patients with hypertension and cerebrovascular insults (37). Infarction in the distribution of the vertebral-basilar circulation has been reported more often than in the area supplied by the carotids (67). The incidence of cerebrovascular accidents in patients thought to have benign essential hypertension is 28 per cent (70), although as many as 58 per cent (71) of patients with hypertension were reported to have acute cerebral syndromes. The incidence of hypertension in several published series of patients with "strokes" is shown in Table II. It was found to be 50 per cent in the present series and 63.4 per cent in a recently reported series of 172 patients (72).

There are two probable explanations for the occurrence of ischemic brain

disease in patients with hypertension. It has been clearly established that hypertension predisposes to cerebral atherosclerosis since a definite increase in the degree of cerebral atherosclerosis has been found in hypertensive patients as compared to normotensive patients of the same ages (23). The use of antihypertensive agents and other causes for abrupt reduction of blood pressure, even to normal levels may also be contributing factors.

CONGENITAL HEART DISEASE

Cerebrovascular accidents have also been reported in a variety of congenital heart lesions (73–76), although more frequently with those associated with cyanosis. The possible pathophysiologic mechanisms include hypoxia, polycythemia, relative anemia and paradoxic embolization.

HEMATOLOGIC DISEASE

Polycythemia is often cited as a contributing factor to cerebrovascular insufficiency. The reported incidence of cerebrovascular accidents in patients with polycythemia varies from 5 per cent to 19 per cent (77). In a recent report of 511 patients with polycythemia, there were 48 cerebrovascular accidents, of which 17 occurred before the polycythemia was recognized (77). The frequent occurrence of transient ischemic cerebral episodes in patients with polycythemia has been stressed recently (78). Intermittent cerebral artery insufficiency has also been reported in association with severe anemia (79), and anemia has also been implicated in more prolonged brain ischemia or infarction (21, 22). Cerebral infarction may also occur during the course of various hemoglobinopathies (80, 81), thrombotic thrombocytopenic purpura (82), macroglobulinemia (83) and other blood diseases. The clinical picture of cerebral ischemia or infarction may at times be simulated by an intracranial hemorrhage related to a defect in coagulation (84) or the demyelinating process associated with reticulo-endothelial disorders (85).

TOXIC-METABOLIC STATES

The production of focal cerebral signs from hypoglycemia has been documented both at the bedside (86, 87) and in the laboratory (87). The explanation usually offered to explain this phenomenon is that a pre-existing (latent) focal cerebral lesion has been made apparent. For several years now, neurologists at this hospital have used intravenous amobarbital as a means of eliciting subclinical neurologic signs. It has thus been possible to elicit a previously unrecognized hemiparesis (88) or focal sensory defect (89) in many patients with a variety of brain lesions. Patients with cerebrovascular disease have had "positive amytal tests" as often as patients with brain lesions of other etiologies. A similar effect, the production of previously latent cerebral signs, has also been noted in patients with high fever, hypoxia, electrolyte imbalance, carbon monoxide intoxication (22) and several other toxic-metabolic disturbances. It is possible that this nonspecific "amytal effect" may be another possible explanation for the occurrence of focal cerebral signs during a period of systemic hypotension (see above).

The exact role played by diabetes mellitus in ischemic brain disease is still uncertain, although it has been shown (99) that diabetes predisposes to cerebral atherosclerosis. In a recent study of 349 diabetics, 5.7 per cent were thought to have had cerebrovascular accidents. The majority of these patients, however, were also hypertensive. Diabetes was present in 32 per cent of the patients in the present series and in 20 per cent of 172 patients in another recently reported series (72).

Other metabolic conditions, including hypercholesterolemia, hyperlipemia, uremia and myxedema, have at times been cited as contributing to ischemic brain disease.

SYSTEMIC INFECTIONS

In recent years, the occurrence of carotid and cerebral artery occlusions from invasion by the fungus causing mucormycosis has been recognized (91). Chronic infectious processes such as syphilis and tuberculosis may also produce an obliterative endarteritis with resultant cerebral infarction. We have seen a patient (not included in the present series) with an angiographically verified middle cerebral occlusion from tuberculosis. There have been several reports of a cerebrovascular accident as the initial manifestation of a generalized viral illness, such as measles (92). Autopsy study has revealed infarction secondary to vascular occlusion, rather than an "allergic" demyelinating process. Septic arteritis during the course of bacterial meningitis may also result in focal infarction. Numerous parasitic diseases such as malaria, trichinosis, paragonimiasis, schistosomiasis and typhus (2) may also involve the cerebral vessels with subsequent cerebral ischemia and infarction.

MISCELLANEOUS SYSTEMIC DISEASES

Cerebral infarction and ischemia may be early manifestations of disseminated lupus erythematosus (93, 94), temporal arteritis (95) and rarely periarteritis nodosa (2). Cerebral endarteritis as part of rheumatic fever has been described (96), and a cerebrovascular accident as the initial manifestation of histologically verified thrombo-angiitis obliterans has been reported (97). Other rarer types of cerebral arteritides have also been suggested (98).

CONCLUSIONS

While there are a large number of systemic and some local conditions which may contribute to ischemic brain disease, the majority of these states (*e.g.* diabetes, hypertension, arteriosclerosis) are usually well recognized prior to the onset of signs of cerebrovascular disease. There are, however, a significant number of patients who may first seek medical attention because of an acute cerebral insult which antedates awareness of the predisposing condition.

The present series of 100 consecutive patients with ischemic and occlusive brain disease thus includes 3 with initially unrecognized acute myocardial infarctions, 12 with previously undetected diabetes mellitus, 7 without prior knowledge of hypertension, 6 with new cardiac arrhythmias and a few who were unaware of blood loss, orthostatic hypotension and other abnormalities. These

conditions were found in patients on both the ward and private services and were not previously known by the patients or their physicians. Other patients, not included in this series, who were admitted to The Mount Sinai Hospital for acute cerebrovascular accidents and were later found to have polycythemia vera (77), disseminated lupus erythematosus (94) and hemorrhagic disorders (84) have been reported elsewhere. We have seen still other patients who were admitted with a typical "stroke" syndrome and were subsequently found to have syphilis, mitral stenosis, subacute bacterial endocarditis and other treatable basic diseases.

Recognition of these contributing conditions is also important for the treatment of ischemic brain disease. Thus, systemic hypotension in a patient with a cerebrovascular accident should always be treated promptly with vasopressors, and the cause of hypotension sought out and corrected. Therapy for cardiac arrhythmias and congestive heart failure should likewise be instituted at an early time. The recognition and elimination of a source for systemic embolization may prevent further cerebral insults. Mechanical obstruction of a great or extracranial vessel may be corrected surgically or, at times, by immobilization of the neck. Reduction of the hematocrit may improve the signs and symptoms of cerebral ischemia in the patient with polycythemia, as may blood transfusions in the patient with severe anemia. Hypoglycemia must be treated vigorously and insulin administered cautiously to patients with diabetes. An attempt should be made to correct hypoxia, fever, electrolyte abnormalities and any other toxic-metabolic state. Antibiotics and other antimicrobial therapy are necessary for the treatment of an infectious cerebral arteritis, and corticosteroid therapy may be helpful for the inflammatory cerebral arterides of other etiologies.

SUMMARY

One hundred consecutive patients with occlusive or ischemic cerebrovascular disease were studied for possible predisposing conditions. Forty-one had definite evidence of cardiac disease, 50 were hypertensive, 32 were found to have diabetes mellitus and 16 had possible hypotensive episodes.

Significant, previously unrecognized diseases included acute myocardial infarction in 3 patients, diabetes mellitus in 12, hypertension in 7 and cardiac arrhythmias in 6.

The significance, pathogenesis and treatment of possible systemic and local conditions contributing to ischemic and occlusive brain disease is discussed.

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RADIOLOGICAL NOTES

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CASE NO. 214

A 71 year old female was hospitalized with a two year history of increasing constipation and intermittent episodes of abdominal pain radiating to the right flank. The patient had one episode of melena within the week before her admission. Physical examination revealed no significant abnormalities. The abdomen was soft and non-tender and no masses were palpated. Radiographic examination of the chest was normal. Barium enema was performed which demonstrated a short eccentric persistent segment of narrowing in the mid-ascending colon (Fig. 1A). There was a suggestion of an overhanging edge on its superior border (Fig. 1B). On some of the barium-filled and air contrast studies, the area of stenosis appeared to change slightly in caliber from barely 1 mm to 3 mm in size. The mucosal pattern was obliterated within the stenotic portion of the lesion, suggesting ulceration. There was no evidence of antigrade or retrograde obstruction. The remainder of the ascending colon and terminal ileum appeared normal. No extrinsic masses were noted indenting the colonic outlines. Laparotomy was then undertaken and an ileocolic resection was performed. The pathologic specimen revealed a napkin-ring lesion 6 cm distal to the ileocecal valve. The mucosa over the lesion was denuded and the wall of the bowel was markedly thickened. A discrete 4 cm flat ulceration was noted in its center. The pathologic diagnosis was tuberculous ulcerative segmental colitis with stenosis. The adjacent lymph nodes showed granulomas, and acid fast bacilli were identified. The patient was placed on antituberculous therapy and had an uneventful recovery.

DISCUSSION

Intestinal tuberculosis is a rare condition in the absence of active pulmonary disease (1). With a negative chest x-ray the diagnosis of an intestinal lesion as being tuberculous in nature presents a most difficult problem. In a series of cases reviewed by Hoon *et al.*, 9 out of 58 cases had negative chest x-rays (2). In Kogan and Janowitz's series, 2 out of the 7 patients had normal chest roentgenograms (3). Tuberculous lesions of the gastrointestinal tract usually localize in the ileocecal region. This location accounts for 85 per cent of the cases quoted in most of the large series (4). The presence of deep or superficial ulcerations in the tuberculous lesions accounts for the marked spasm usually seen radiographically in this disease.

The sign described by Stierlin (5) in ileocecal tuberculosis is a manifestation of marked irritability secondary to ulceration with failure of this portion of the colon to retain barium. However, this sign is not pathognomonic of intestinal

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tuberculosis and can be seen in association with active inflammation in or around the cecum from any other cause. On occasion, the colon can be diffusely involved with tuberculous colitis at which time the roentgen appearance is similar to granulomatous or even diffuse nonspecific ulcerative colitis. Isolated lesions like

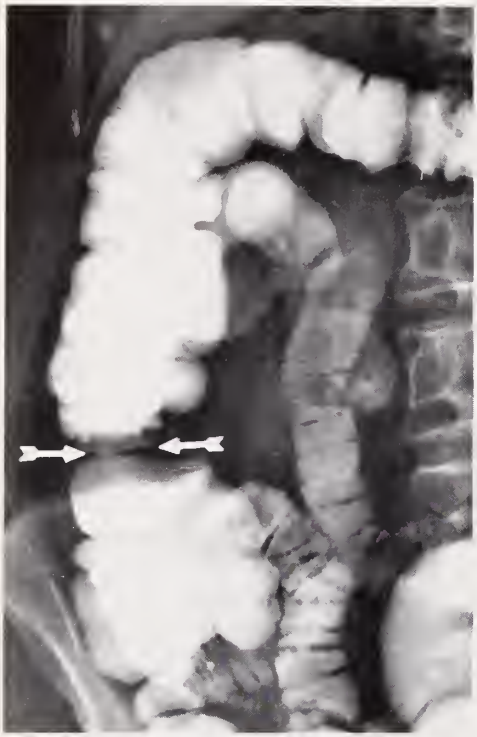

Fig. 1A.

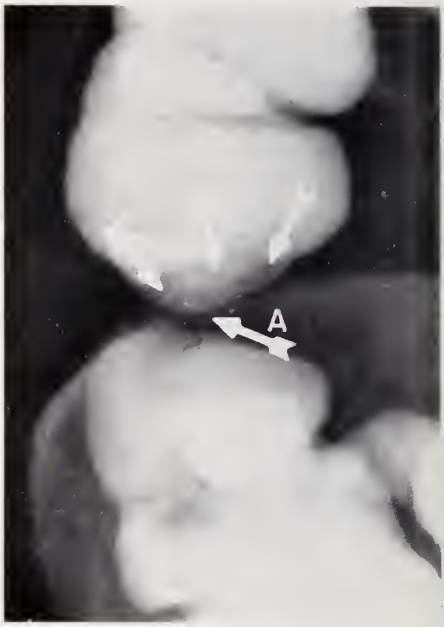

Fig. 1B.

Case 214, Fig. 1A. Barium enema reveals a short area of narrowing in the ascending colon just above the ileocecal region (between arrows). The lumen through the lesion is eccentric in position. There is no evidence of retrograde or antigrade obstruction.

Case 214, Fig. 1B. Spot film of the ascending colon in the course of the same examination again reveals the stenotic area with an eccentric lumen (arrow A). In the upper portion of the lesion there is a suggestion of an overhanging edge (along arrows). The normal mucosal pattern is obliterated suggesting ulceration.

the one presented in this case are very rare, especially when the ileocecal region is normal. These short stenotic segments of colonic tuberculosis must be differentiated from annular carcinomas of the colon. The most important point in favor of the diagnosis of tuberculosis is the demonstration of a small amount of changeability of the caliber of the stenotic lumen. Even a minimal amount of distensibility is much against the roentgen diagnosis of infiltrating carcinoma. On the other hand, this finding is to be expected in tuberculosis, as much of the

narrowing is secondary to marked spasm resulting from active ulceration in the involved segment.

Case Report: Tuberculosis of the ascending colon.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Samuel H. Klein.

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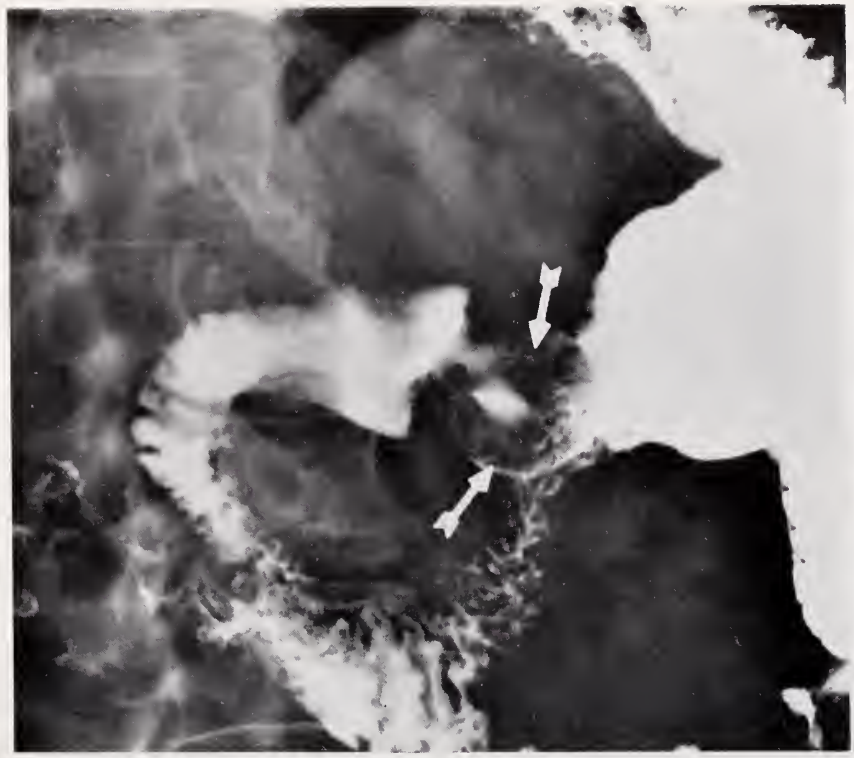
CASE NO. 215

A 70 year old male experienced midepigastric pain for three months, occasionally radiating to the back. Associated with these symptoms were moderate anorexia and a 5 pound weight loss. There was no evidence of hematemesis or melena. Physical examination revealed considerable skin pallor but no icterus. On abdominal examination the liver was palpated three fingers below the right costal margin, but there were no masses or other organ enlargement. Barium meal examination was performed and demonstrated a filling defect 4 cm in diameter within the antrum of the stomach with a sharply demarcated diamond-shaped 1 cm central ulceration (Figs. 1A, 1B). The mucosal pattern of the stomach just proximal to this lesion appeared to be intact. The lesion was sharply delineated both proximally and distally. There was no evidence of gastric obstruction. The duodenal bulb was normal. The duodenal sweep was of normal width but there was evidence of pleating of the mucosal folds in the medial aspect of the descending duodenum (Fig. 1C). The findings within the stomach suggested a submucosal lesion with a central ulceration in the distal antrum. The findings in the duodenal sweep were those of a mass in the head of the pancreas. Gastroscopy was then performed and a 4 mm stellate-shaped gastric ulcer was noted just beyond the re-entrant angle with a grayish base and hemorrhagic border. There was no nodularity at the base of the ulcer. Peristalsis appeared normal. Laparotomy was then perfomed, at which time an orange-sized mass was noted to be present in the head of the pancreas. In addition, a separate independent freely movable submucosal mass was noted in the distal portion of the gastric antrum. A gastric antrectomy was performed to remove the submucosal mass and because of the presence of a carcinoma of the pancreas a diverting gastrojejunostomy was performed with a cholecystojejunostomy. Pathological



Case 215, Fig. 1A. Right anterior oblique view of the stomach filled with barium reveals a sharply demarcated smooth filling defect in the distal portion of the antrum (between arrows). There is a diamond-shaped central ulceration. There is no evidence of gastric obstruction. The base of the duodenal bulb appears normal.

Case 215, Fig. 1B. Pressure spot film of the lesion during the course of the same examination again demonstrates the sharp proximal edge of the lesion (along arrows). The peculiar central ulceration (arrow A) is seen to better advantage. It is noted to be relatively large and angular in contour.

report revealed the gastric lesion to be a metastatic adenocarcinoma to the submucosa. The mass in the head of the pancreas was biopsied and also revealed adenocarcinoma, and was probably the site of origin of the primary malignancy.

Case 215, Fig. 1C. Examination of the distal stomach in the right anterior oblique projection again reveals the gastric lesion described above with its central ulceration (arrow A). At this time, there is evidence of extrinsic pressure upon the medial aspect of the duodenal sweep suggesting a mass lesion in the head of the pancreas (along arrows).

DISCUSSION

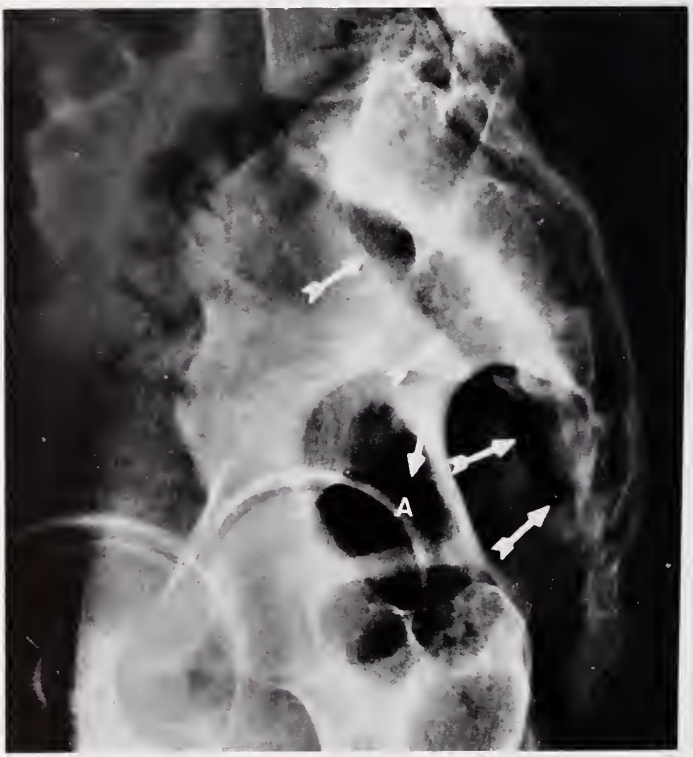
The finding of a submucosal metastasis to the stomach is unusual. However, recently we have come to recognize this entity more frequently. Multiple submucosal metastases to the stomach have been reported in malignant melenomas, carcinoma of the breast and carcinoma of the lung. Single metastases seem to be rarer. The differential diagnosis includes benign submucosal tumors, the most common of which are myomas. However, these benign submucosal tumors usually have small punched-out central ulcerations as opposed to the case presented here where the ulcer was bizarre in shape, being stellate and relatively larger than would be expected with a myoma. Pancreatic rests enter into the differen-

tial diagnosis but the central patch of barium, representing the opening of the independent pancreatic duct, is usually much smaller than in the present case. On occasion, one can have difficulty in differentiating a large smooth ulcer mound surrounding a benign gastric ulcer.

Case Report: Isolated submucosal gastric metastasis from carcinoma of the pancreas.

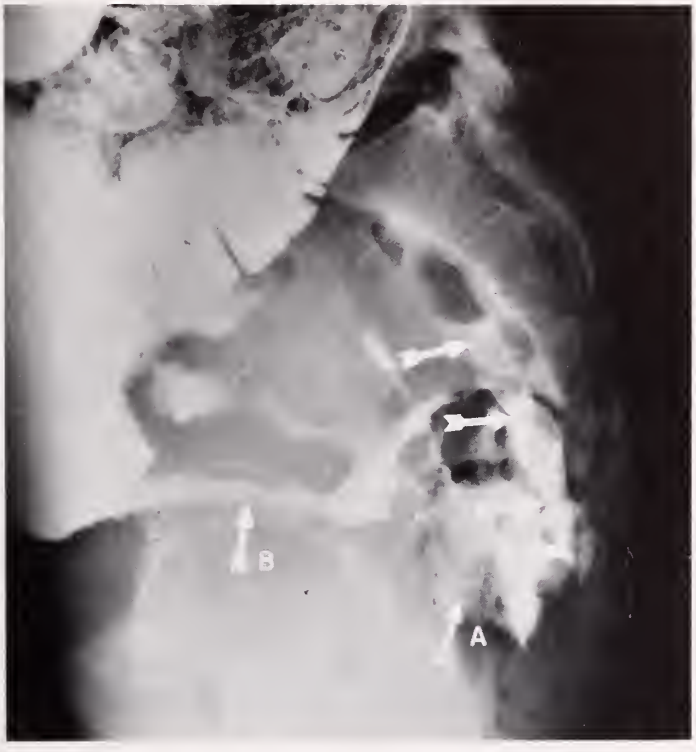
CASE NO. 216

A 34 year old male was admitted to the hospital because of severe pain in the lumbosacral region radiating to both legs, associated with difficulty in walking. The patient had known regional enteritis for one year and had been well controlled on steroid therapy. The patient experienced a ten pound weight loss in the previous six months. Appetite was good. There had been no diarrhea. Physical examination revealed no localized tenderness in the lumbosacral spine. The abdomen was soft without evidence of deep tenderness. Both legs were noted to be externally rotated at the hips and forced internal rotation of the lower extremities produced severe pain.



Case 216, Fig. 1. Lateral view of the lumbosacral spine reveals a peculiar elongated air-collection just anterior to the sacral hollow (along arrows) with a smooth anterior border. The air in the rectal ampulla (arrow A) is separated from the presacral air by a soft tissue space approximately 2 cm wide.

Radiographic examination of the lumbosacral spine revealed no bony abnormality. On the lateral view of the sacrum, there was a peculiar air collection anterior to the sacral hollow with smooth borders (Fig. 1). This air-conditioning space was separated from the gas-filled rectal ampulla by a soft tissue space approximately two cm wide. Because of this unusual air collection, a diagnosis



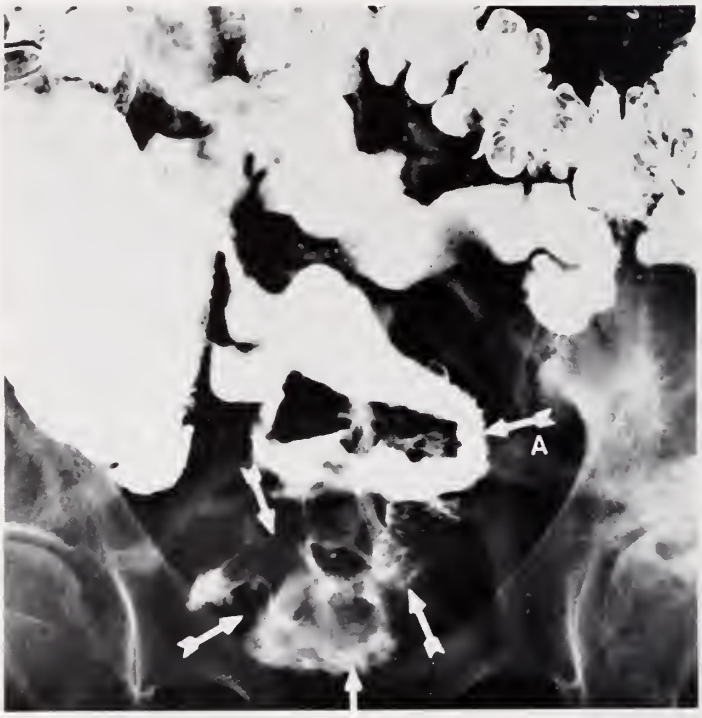
Case 216, Fig. 2A. Lateral view of the pelvis during a small bowel examination shows an amorphous collection of barium just anterior to the sacrum (along arrows) which corresponds to the air-conditioning shadow seen in Fig. 1. The barium lies within the posterior portion of the pelvic abscess. The inferior extension of the pelvic abscess is noted anterior to this (arrow A). A diseased loop of distal ileum is noted in the vicinity of the pelvic abscess (arrow B).

of presacral pelvic abscess was advanced. Small bowel examination was then performed which confirmed this impression. Barium entered a large presacral abscess (Figs. 2A, 2B) which corresponded in distribution to the abnormal air collection noted in the lateral view of the sacrum. A distal loop, involved with regional enteritis, was noted to connect with the pelvic abscess.

DISCUSSION

The incidence of pelvic abscesses and fistulae in a large series of granulomatous ileitis is approximately 15 per cent (1). The interest in the case presented was

the ability to visualize the air-conditioning abscess cavity in the presacral region on the plain films of the spine. This became of considerable practical clinical help as the patient was originally considered to be suffering from an orthopedic problem related to the hips. A barium meal examination confirmed the presence of the pelvic abscess secondary to fistulization from a distal ileal loop involved with regional ileitis. The inability of the patient to walk normally and to inter-



Case 216, Fig. 2B Frontal projection of the pelvis during the course of the small bowel examination reveals the diseased loop of ileum in the midportion of the pelvis (arrow A). The amorphous barium within the pelvic abscess is seen inferior to this loop (between arrows).

nally rotate the lower extremities was the result of ileopsoas spasm secondary to the deep pelvis inflammatory mass.

Case Report: Presacral pelvic abscess secondary to regional ileitis.

ACKNOWLEDGMENT

This case is presented through the courtesy of Drs. Alexander Richman, Edward Jemerin and Frederick Marek.

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CASE NO. 217

A 64 year old male was admitted to the hospital because of hematemesis and melena of four days' duration.

For years prior to admission, the patient presented with a mass of lymph nodes in the left cervical region associated with a neoplastic lesion of the left tonsil. A biopsy of the lymph nodes was reported as reticulum cell sarcoma. The tonsil and the cervical region were successfully treated with Cobalt-60 radiation. Three years prior to admission, lymph node enlargement in the right cervical region was treated with Cobalt-60 radiation. One and one-half years prior to admission, the patient noted progressive severe upper gastrointestinal symptoms with pain, weight loss, weakness, fatigability and severe episodes of melena. Barium meal examination revealed a large ulcer in a mass high on the posterior wall of the stomach which was thought likely to be lymphomatous. Radiation therapy was instituted and the patient received a fractionated dose of 3,500 rads to the stomach.

The patient was then well for almost one year but gastrointestinal symptoms gradually recurred in the weeks prior to admission. Barium meal examination was again positive. Radiation therapy was reinstituted but hematemesis and melena in the next few days led to hospitalization.

Repeat barium meal examination in the hospital revealed a large irregular ulceration high on the posterior wall of the stomach which measured 5 cm in greatest diameter. The ulcer projected into a large mass which occupied the posterior wall of the stomach and the retrogastric region (Figs. 1A, 1B).

The patient received numerous blood transfusions for persistent bleeding and borderline shock. Emergency gastroscopy using the fiberscope was unsuccessful in visualizing the lesion. Surgical intervention was deemed mandatory.

Through a thoracoabdominal incision, a very large tumor mass in the left upper quadrant was visualized. The mass involved the hilum of the spleen, the tail of the pancreas, the transverse mesocolon and the colon itself, and the greater curvature-posterior wall of the stomach. A large, deep ulceration was noted high on the posterior wall of the stomach which had eroded through the wall and which extended deep into the mass. Vigorous bleeding was observed at the base of this ulceration. An en bloc resection was performed including a proximal gastrectomy, distal pancreatectomy, splenectomy and partial colectomy, with esophago-gastrostomy and colocolostomy. Histologic examination of the specimen confirmed the diagnosis of reticulum cell sarcoma.

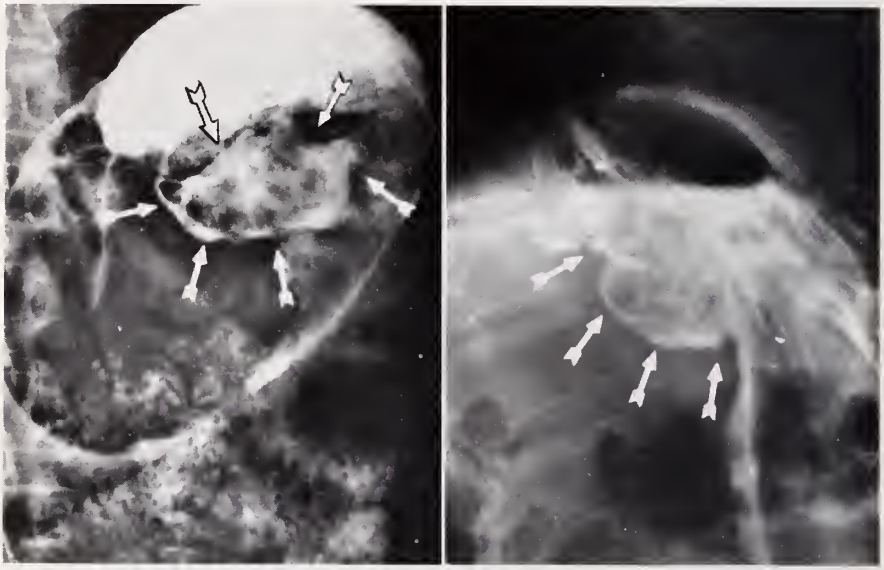
The patient had a stormy postoperative course complicated by an anastomotic leak from the colocolostomy with resultant left fecal empyema. He expired shortly after a drainage procedure to the left chest on the eighth postoperative day. Postmortem examination was refused.

DISCUSSION

Lymphomatous involvement of the stomach may be primary or part of a disseminated process. The incidence of primary gastric lymphoma is variably stated in the literature to be between 0.5 per cent and 6 per cent of all malignant

gastric neoplasms with the true incidence probably around three per cent (1–4). There are many more cases of secondary than of primary involvement found at postmortem examination; however, the percentage of these cases in which significant clinical involvement occurs is not known. The usual histologic types are small cell lymphosarcoma, reticulum cell sarcoma and lymphoblastoma (5). Hodgkin's disease also occurs, but involvement of the stomach with this disease is much less common than with the other varieties (3, 6).

The prognosis in cases of primary gastric lymphoma is much better than with gastric carcinoma; five year survivors range between 25 per cent and 50

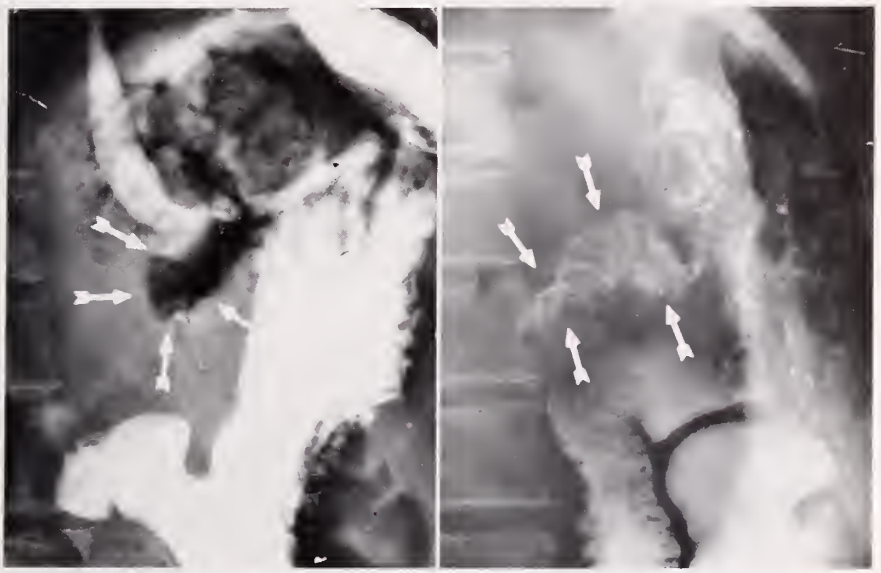


Case 217, Fig. 1A. Anteroposterior supine radiograph of the stomach shows a 5 cm irregular ulcer crater high on the posterior wall filled with barium and seen through the air distended body (arrows). 1B. Erect lateral radiograph shows the large ulcer crater projecting into a mass which occupies the posterior wall of the stomach (arrows).

per cent, or even greater in selected case material (1, 3, 7, 8). Treatment of choice is surgical with or without complimentary radiation therapy; however, radiation alone can cure the disease (9, 10). The prognosis in cases with secondary involvement is quite poor. Here, radiation therapy is the treatment of choice and surgery is not indicated generally. Surgical intervention in the case presented was dictated by the urgent clinical situation of massive bleeding.

A number of different roentgen patterns have been described (2, 3, 5). These include infiltration of the gastric wall with an area of rigidity or narrowing, ulceration within a tumor mass (may be multiple), simple ulceration (may be multiple), polypoid tumor mass of fairly large size, multiple (rarely single) small submucosal nodules, and generalized or local rugal hypertrophy. With multiple nodules or rugal hypertrophy, the diagnosis of lymphoma should be considered

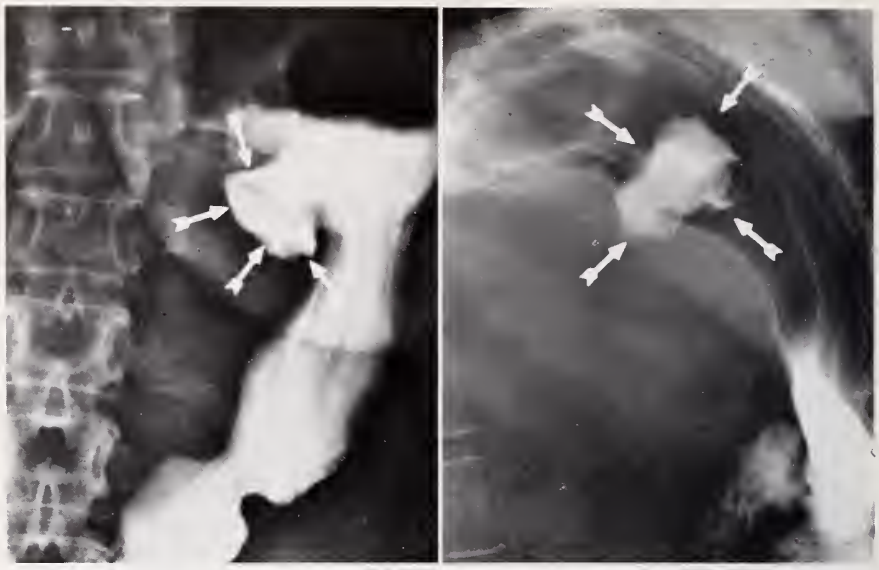
strongly; with the other varieties the lesion is indistinguishable from carcinoma. One important point of differentiation is the propensity with which lymphoma crosses the pylorus to involve both the stomach and the duodenal bulb; this is uncommon with carcinoma. The appearances described above culled from the literature on the subject, appear to apply mainly to cases with primary involvement. No specific references to radiographic differences between primary and secondary varieties have been uncovered in a brief review of the recent English literature.



Case 217, Fig. 2. Another case of reticulum cell sarcoma involving the stomach presented through the courtesy of Dr. Ezra Greenspan. 2A. Right anterior oblique radiograph of the stomach shows an irregular collection of air outside the confines of the stomach posteriorly (arrows). 2B. Lateral radiograph shows barium outlining an irregular cavity in a retrogastric mass (arrows).

The case presented here emphasizes a particular combination of roentgen features (Fig. 1), also apparent in radiographs from two additional cases (Figs. 2, 3). All three are cases of secondary gastric involvement and each presents a large, deep irregular ulceration which penetrates completely through the posterior gastric wall into a large retrogastric mass. We have come therefore to regard secondary lymphoma as a likely diagnosis with this combination of findings, although no doubt primary disease can also produce this picture. Differential diagnosis should also include primary gastric carcinoma, primary gastric sarcoma of other varieties such as leiomyosarcoma, pancreatic carcinoma with gastric invasion and other unusual malignant retroperitoneal neoplasms with secondary gastric involvement.

Case Report: Secondary gastric lymphoma. Presentation of three cases.



Case 217, Fig. 3. A case of giant follicle lymphoblastoma involving the stomach presented through the courtesy of Dr. Louis Wasserman. 3A. Erect posteroanterior radiograph of the stomach shows a large irregular ulcer crater projecting medially from the posterior wall-lesser curve near the cardia (arrows). 3B. Lateral radiograph again shows the ulceration (arrows). The stomach and duodenum are displaced anteriorly by retroperitoneal mass.

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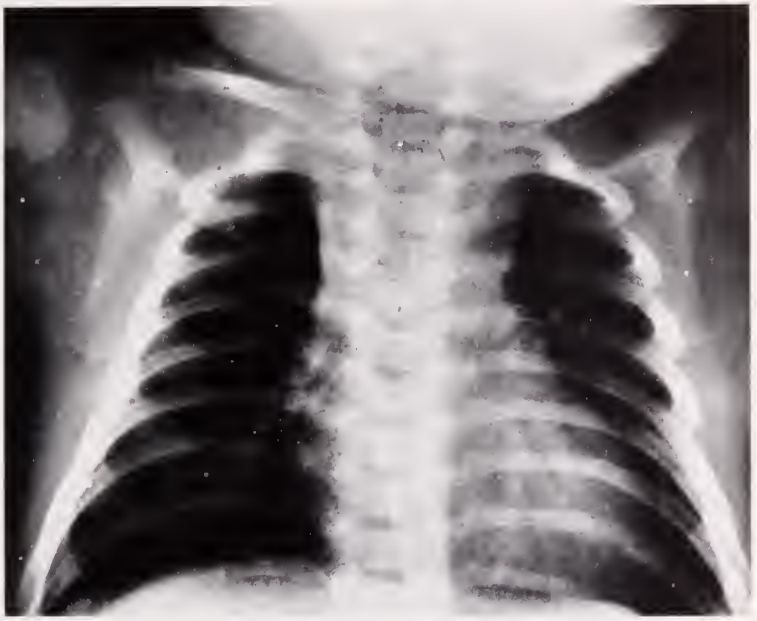
CASE NO. 218

An eight week old male infant was admitted to the hospital with respiratory distress and fever. The infant was well until two days prior to the admission when the mother noted fever to 105° and mild cough. Physical examination revealed a few nonlocalized rhonchi but no respiratory distress. Tetracycline therapy and steam inhalations were prescribed. Thirty-six hours later the mother reported increasing respiratory distress. Repeat examination revealed a respiratory rate of 40 to 50 per minute with marked prolongation of the expiratory phase of res-

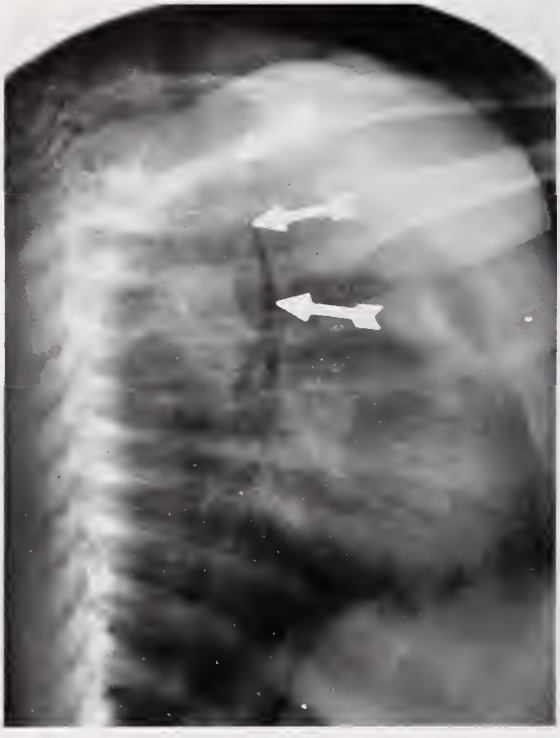


Case 218, Fig. 1A. Posteroanterior radiograph of the chest shows no abnormality in the heart and lungs. The tracheal air column is not seen. The bulge to the contour of the left superior mediastinum, felt to be normal originally, is significant in retrospect.

piration, expiratory wheezing, flaring of the alae nasi, and subcostal retractions. The temperature was 101°. The patient was admitted to the hospital with a clinical diagnosis of bronchiolitis and placed in oxygen in a croup-tent. It was then observed that the infant became more comfortable with a change in position of the head and thorax. The white blood count was 27,000 with a shift to the left.

Radiographic examination of the chest revealed no abnormality in the heart and lungs (Figs. 1A, 1B). However, the tracheal air shadow was noted to be markedly thinned and bowed anteriorly as seen in the lateral view; the air column could not be made out in the frontal view. A barium swallow was then administered and the radiographs were repeated (Figs. 2A, B). The upper thoracic esophagus was markedly deviated anteriorly and to the right along with the

trachea. A slight bulge of the left superior mediastinum, which was felt to be within the range of normal on the plain film study, was now considered to be a significant shadow. The dorsal spine showed no abnormality. The diagnosis advanced was that of a soft tissue mass in the posterior superior mediastinum displacing the esophagus and trachea causing marked narrowing of the airway and respiratory distress. In view of the history when available this was thought to represent an esophageal duplication or bronchogenic cyst with secondary infection.



Case 218, Fig. 1B. Lateral radiograph of the chest shows marked thinning and anterior bowing of the tracheal air shadow (arrows).

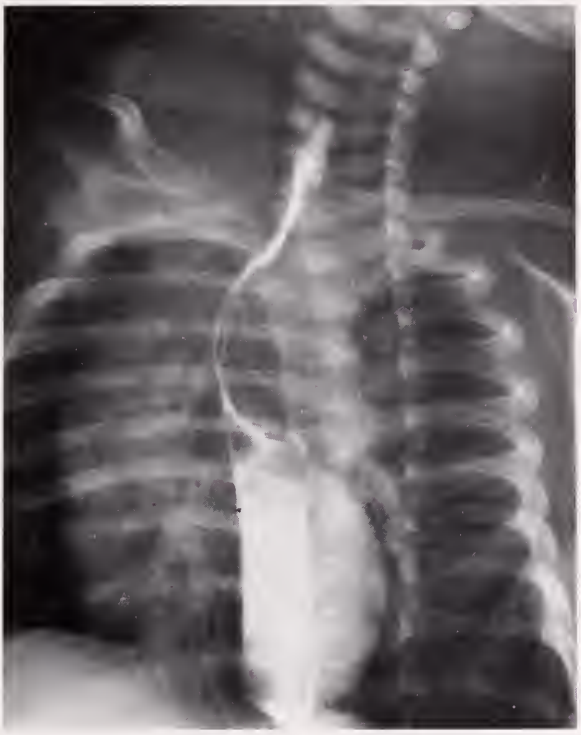
The patient was transferred to a nearby medical center where a thoracotomy and mediastinal exploration were performed. A collection of approximately ten cc of thin purulent fluid was located in the posterior superior mediastinum intimately associated with the posterior wall of the esophagus. The mediastinum was drained and the chest was closed. The child did poorly and expired six hours postoperatively.

Postmortem examination revealed a one inch tear in the posterior aspect of the cervical esophagus. The tear was sealed off by fibrinous exudate. Histologically, fibroblastic proliferation indicated an age of four or five days to the process. No foreign body was noted in the thorax or abdomen.

The history was now reviewed and a source of trauma specifically sought. The father reported having observed an older sibling attempt to feed the infant forcibly with a teaspoon four days prior to death and one day prior to the onset of the illness.

DISCUSSION

Perforation or rupture of the esophagus can be divided into two main categories: traumatic and spontaneous. Traumatic perforation often follows iatro-



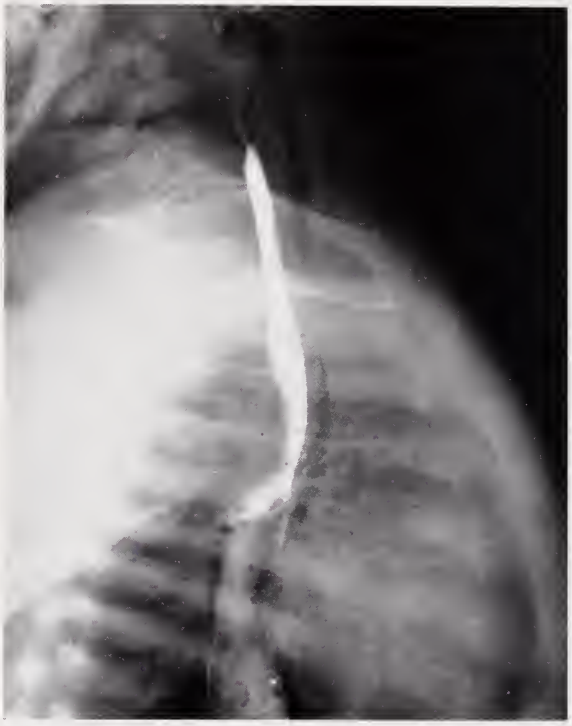
Case 218, Fig. 2A. Left anterior oblique esophagram.

genic instrumentation, such as esophagoscopy, bougienage, or Sengstacken intubation (1). The incidence is increased in cases where organic obstruction is present and in which biopsy is performed. Foreign body perforation should be included in this group. A case has been reported in a newborn following aspiration of secretions with a stiff rubber catheter (2). The case reported here falls into this category, the rupture no doubt having been caused by "trauma" with a teaspoon.

"Spontaneous" perforation usually refers to the Mallory-Weiss syndrome. In this syndrome a longitudinal tear occurs in the lower esophageal segment just above the diaphragm posterolaterally on the left side usually following a bout of retching or vomiting. "Spontaneous" is a poor term for these cases as the mech-

anism of occurrence and numerous contributing factors have been documented both clinically and experimentally (3, 4). A case of this type has been reported in a two month old infant (3). A few rare cases of true "spontaneous" or "agnogenic" perforation have been reported, the youngest in a newborn infant (5).

The clinical course in the case reported here is remarkable. Whereas fever, leukocytosis and respiratory distress are common, respiratory embarrassment due to tracheal compression by an abscess must be quite rare. The lack of addi-



Case 218, Fig. 2B. Lateral esophagram. Both views demonstrate marked displacement of the esophagus anteriorly and to the right along with the thinned tracheal air shadow.

tional clinical signs is unusual; the two cases cited in neonates presented with tension pneumothorax (2, 5).

The usual roentgen findings in esophageal perforation are mediastinal emphysema, pneumothorax, plural effusion and mediastinal widening; none of these was present in this case (4, 6). However, the roentgen findings of a posterior mediastinal mass with its tracheo-esophageal effects are exquisitely demonstrated (Figs. 1, 2). The plain films merit particular attention as regards the tracheal air shadow, as well as the absence of remarkable mediastinal widening or emphysema.

The differential diagnosis of a mass in the posterior mediastinum should in-

clude neurogenic tumor (most common), enterogenous cysts and duplications (including neurenteric cysts with vertebral abnormalities, thoracoabdominal duplication and multiple duplications), bronchogenic cysts, anterior meningocele, prevertebral abscess due to Pott's disease and other unusual neoplasms (7).

Case Report: Traumatic perforation of the esophagus in an eight week old infant.

ACKNOWLEDGMENT

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DR. RALPH COLP AWARD

Dr. John E. Moseley

Dr. Ralph Colp

Dr. John E. Moseley is the recipient of the Dr. Ralph Colp Award for 1962. The award was given for Dr. Moseley's brilliant series of articles in the Journal of The Mount Sinai Hospital on bone changes in hematological disorders.

This award is made by the Dr. Ralph Colp Fund, established by his colleagues and friends in honor of Dr. Ralph Colp, in recognition of his long years of distinguished service to The Mount Sinai Hospital and to American surgery.

Partition Studies of the Neutral 17-Ketosteroids in Klinefelter's Syndrome with a Theory as to the Pathogenesis of the Syndrome

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In 1942, Klinefelter, Reifenstein and Albright described a syndrome characterized by gynecomastia, aspermatogenesis without a-leydigism and increased urinary excretion of follicle stimulating hormone (1). The syndrome was demonstrated by Heller and Nelson to include individuals without gynecomastia and with various degrees of eunochoidism (2). The constant features of the syndrome are small testes, widespread hyalinization of the seminiferous tubules, high urinary titers of gonadotropins and azoospermia. The pathogenesis of the syndrome particularly with respect to the testicular lesion has not been elucidated, although following the introduction of the sex chromatin technique by Barr (3), it was shown that there is a chromatin positive and a chromatin negative form of the disorder. The former is usually associated with an XXY sex chromosomal pattern, the latter with XY. Nelson has claimed that these two variants of the syndrome can be differentiated on the basis of the testicular biopsy (4). In the testes of the subjects with a positive sex chromatin there are seen very small completely hyalinized scars interspersed with occasional large but none the less predominantly small tubules populated by Sertoli and very rare germ cells. The tubules lack the normal architectural organization and the Leydig cells tend to be clumped in areas of unusual size. In contrast, in the testes of the subjects with a negative sex chromatin, the tubules are larger, the degree of tubular sclerosis less marked, spermatogenesis, though impaired, is in progress, and the Leydig cells show less tendency towards clumping and nodule formation.

The peculiar clumping and appearance of the Leydig cells in this disorder plus their apparent increase in number has led to the belief that some abnormality in androgen production may be present. Although data are available on the urinary excretion of the total neutral 17-ketosteroids, there are scant data on partition studies of the androgen metabolites in Klinefelter's syndrome. This report is concerned therefore with such studies. Some values for estrogen excretion have also been included.

METHODS

Partition of the neutral 17-ketosteroids (17-KS) was carried out by a modification of the method of Rubin *et al.* (5). The details of this procedure have been

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previously published (6). Nine subjects with Klinefelter's syndrome were studied. Of these seven were chromatin positive and two were chromatin negative. In the chromatin positive group the diagnosis was based on the clinical picture and the presence of a positive sex chromatin pattern. In almost all of these a high urinary gonadotropin titer and/or a typical testicular biopsy were also available. In the chromatin negative group, the diagnosis was similarly based on the clinical picture, a negative chromatin pattern and in addition a high urinary titer of gonadotropins and a typical testicular biopsy.

In three subjects dexamethasone was administered in a daily dosage of 2.25 mg for seven days and the neutral 17-ketosteroid metabolites measured on the last day of treatment. In the same subjects, at a later date, human chorionic gonadotropin (HCG) was given in a daily intramuscular injection of 5000 IU for a period of three days and the urine obtained on the third day of therapy was partitioned.

Urinary estrogens were estimated in five subjects by the method of Brown (7) and in two patients by the procedure of McAnnally and Hausman (8). Included in the latter is a tenth patient in whom a partition study of the neutral 17-ketosteroids was not obtained.

RESULTS

The urinary excretion of the total neutral 17-ketosteroids varied from 6.0 mg/24 hrs to 15.0 mg/24 hrs, all being within the normal range, although the the values were at the lower end of the normal scale in the oldest subject, aged 78 years, and youngest subject, aged 14 years, and in two others.

The absolute titers of androsterone and etiocholanolone varied from 1.4 to 4.1 mg/24 hrs and 1.1 to 4.9 mg/24 hrs respectively. These values were also within the normal range except that the androsterone values in patients S.B., aged 78 years, and F.E., aged 14 years, were low. The androsterone/etiocholanolone ratio was also normal in all instances, the range being from 0.8 to 1.6.

The percentage of 11-desoxy-17-ketosteroids was reduced, ranging from 36 to

Trivial Names Used in the Text

Dexamethasone: 9α-fluoro-16α-methyl prednisolone
Androsterone: 3α-hydroxy-5α-androstan-17-one
Etiocholanolone: 3α-hydroxy-5β-androstan-17-one
Dehydroepiandrosterone: 3β-hydroxy-5-androsten-17-one
Androstenedione: 4-androstene-3,17-dione
Pregnanediol: 5β-pregnan-3α,20α-diol
Pregnanetriol: 5β-pregnan-3α,17α,20α-triol
Pregnenediol: 5-pregnen-3β,20α-triol
Estrone: 3-hydroxy-1,3,5, (10)-estratriene-16-one
Estradiol-17β:3,17β-dihydroxy-1,3,5, (10)-estratriene
Estriol: 3,16α,17β-trihydroxy-1,3,5 (10)-estratriene
Testosterone: 17β-hydroxy-4-androsten-3-one
Progesterone: Pregn-4-ene-3,20 dione
Pregnenolone: 3β-hydroxy-preg-5-en-20-one
17α-hydroxyprogesterone: Pregn-4-ene-17α-ol-3,20 dione
17α-hydroxypregnenolone: 3β-hydroxy-preg-5-en-17α-ol-20-one

TABLE I

Partition Studies of the Urinary Neutral 17-Ketosteroids (mg/24 hrs) and Estrogen Excretion (μg/24 hrs) in Patients with Klinefelter's Syndrome

Rx	Patient	Age-Yrs	Sex Chromatin	Testicular Biopsy	Gynecomastia	Gonadotropin Titer M. U. U.	Total Estrogens§§ μg	Estrone* (E_1)§ μg	Estradiol* (E_2)§ μg	Estriol* (E_3)§ μg	Total 17-KS mg(%)	β-Fraction (%)	Androsterone mg(%)	Etiocholanolone mg(%)	Total 11-desoxy-17-KS mg(%)	A/E ratio	Androstanol-11,17 dione mg(%)	Etiocholanol-11,17 dione mg(%)	17-KS more polar than etiocholanol-11,17 dione mg(%)	Total 11-oxygenated 17-KS mg(%)
Control	L.F.	29	+	Yes	+	+100		5.5	9.9	12.3	13.5	9.0	4.1 (30)	2.6 (19)	6.7 (49)	1.6	1.3 (10)	1.3 (10)	1.5 (11)	4.1 (30)
HCG, 5,000 IU qd × 3d											12.7	5.6	2.7 (21)	3.3 (26)	6.0 (48)	0.8	1.2 (10)	1.0(8.0)	2.3 (18)	4.5 (35)
Dexamethasone 2.25 mg qd × 7d											9.7	5.8	3.3 (35)	1.9 (20)	5.2 (59)	1.7	2.3 (24)		1.1 (11)	3.4 (35)
Control	A.W.	15	+	Yes	+	+200		4.9	1.3	1.5	13.6	3.0	2.9 (21)	2.0 (14)	4.9 (36)	1.5	0.9 (6)	2.6 (19)	1.3 (10)	4.8 (35)
HCG, 5,000 IU qd × 3d											13.9	3.1	3.1 (23)	1.9 (14)	5.0 (36)	1.6	1.0 (7)	2.2 (16)	2.0 (14)	5.0 (36)
Dexamethasone 2.25 mg qd × 7d											5.6	7.0	1.4 (25)	1.0 (18)	2.4 (43)	1.4	0.5 (9)	0.6 (11)	0.8 (14)	1.9 (34)
Control	S.B.	78	−	Yes	+	+100					6.9	17.4	1.4 (20)	1.3 (19)	2.7 (39)	1.1	0.4 (6)	0.4 (6)	1.4 (20)	2.2 (32)
HCG 5,000 IU qd × 3d											5.7	9.0	2.3 (40)	0.9 (16)	3.2 (57)	2.6	0.2(3.0)	0.4 (7)	0.4 (7)	1.0 (17)
Dexamethasone 2.25 mg qd × 7d											4.3	16.4	1.0 (23)	0.8 (19)	1.8 (42)	1.3	0.6 (14)	0.3 (7)	0.6 (14)	1.5 (35)
	J.W.	26	+	Yes, not available	0	+10 −50					11.3	1.7	3.0 (27)	2.2 (20)	5.2 (46)	1.4	0.8 (7)	0.7 (6)	0.7 (6)	2.2 (19)
	A.P.	17	+	Yes	0	+100	31.6				8.9	7.3	3.1 (35)	2.3 (26)	5.4 (61)	1.4	0.5 (6)	0.5 (6)	0.7 (8)	1.7 (20)
	J.M.	38	+	Yes	0	>52					15.0	8.0	3.9 (26)	2.8 (19)	6.7 (45)	1.4	1.2 (8)	1.0 (7)	1.9 (13)	4.1 (27)
	J.L.	23	+	No	+	+100		4.9	0	10.9	14.6	0.7	3.9 (27)	4.9 (34)	8.8 (60)	0.8				3.5 (24)
	C.M.	26	−	No	+	+200	83.0													
	F.P.	26	−	Yes	0	+100		4.1	1.7	10.3	8.8	8.0	2.9 (33)	2.4 (27)	5.3 (60)	1.2				1.8 (21)
	F.E.	14	+	No	+	+10 −50		3.1	1.1	27.7	6.0	20.0	1.6 (27)	1.1 (18)	2.7 (45)	1.5	0.3 (5)	0.3 (5)	1.0 (17)	1.6 (27)
	A.S. nl	27									13.5	1.1	3.8 (28)	4.0 (30)	7.8 (58)	1.0	0.9 (7)	0.8 (6)	3.5 (26)	5.2 (39)
	R.K. nl	24									8.4	7.2	2.3 (27)	3.3 (39)	5.6 (67)	0.7	0.3 (4)	0.3 (4)	1.5 (18)	2.1 (25)
	E.H. nl	22									12.2	1.0	3.3 (26)	3.6 (27)	6.9 (53)	0.9	1.3 (10)	0.7 (5)	2.2 (17)	4.2 (32)
	8 nl men‡	19 to 35											3.36 ± 0.57	3.89 ± 0.59			0.35 ± 0.06	0.51 ± 0.07	0.73 ± 0.13 + 0.35 ± 0.11	

* Brown Method (7) Normal Males: E_1 3–8.2 μg/24 hrs. E_2 0–6.3 μg/24 hrs. E_3 0.8–11 μg/24 hrs.

† Method of McAnnally and Hausman (8) Normal Males 0–40 μg/24 hrs.

‡ Data of Rubin *et al.* (29).

§ Biochemical Procedures, Calif.

61. The absolute values ranged from 2.7 to 8.8 mg/24 hrs. The values for the total 11-oxy-ketosteroids varied from 1.6 to 4.8 mg/24 hrs.

The administration of chorionic gonadotropin in the dosage employed was without any constant effect on the urinary excretion of the total neutral 17-ketosteroids or the various fractions of the partition.

The administration of dexamethasone resulted in a reduction of the total neutral 17-ketosteroids as well as of the total 11-desoxy and 11-oxy-ketosteroids. However, significant amounts of both groups of metabolites remained.

Total urinary estrogen was increased in one chromatin negative subject (C.M). In one chromatin positive subject, urinary estradiol and estriol were increased. In two other subjects, one chromatin positive and one chromatin negative, urinary estriol was at the upper limit of normal, and in a third it was increased.

DISCUSSION

The pathogenesis of the testicular lesion in Klinefelter's syndrome has not been delineated. The apparent increase in the number of Leydig cells and their altered appearance suggested that the interstitial cells might be excessively stimulated because of primary excessive pituitary activity or to compensate for inadequate Leydig cell function. These investigations as well as others now in progress were undertaken to explore these possibilities in the light of several clues that may bear on the pathogenesis of the testicular lesion.

Maddock and Nelson, in 1952, demonstrated that the administration of chorionic gonadotropin to adult men with functioning testes resulted in alterations which in retrospect markedly resemble those seen in Klinefelter's syndrome (9). There was a decrease in the size of the tubules, an increase in peritubular fibrosis, hyalinization of the basement membrane, necrosis of germinal cells and cessation of spermatogenesis. In none of the patients studied was there any alteration in the number or appearance of the Sertoli cells. There was a substantial increase in the number of Leydig cells which were small, dark staining, heavily granulated and contained increased numbers of lipid droplets. In addition bilateral gynecomastia was induced in two of the five patients studied. During the course of administration of chorionic gonadotropin, the urinary titer of the neutral 17-ketosteroids usually rose modestly (2×) whereas the urinary estrogen levels rose markedly (5 to 16×).

The effects of estrogen on the testes are also pertinent and have been studied by several workers who in general support the findings of de la Balze and his associates (10). The alterations may vary from slight to intense and include reduction in the tubular diameter and lumen, arrested spermatogenesis with hypospermatogenesis, thickening of the tubular wall with fibrosis and hyalinization, reduction in the quantity of Leydig cells and intense fibroblastic proliferation. It is of note that similar changes have been found in the testes of patients with destructive lesions of the pituitary and de la Balze and his associates suggested that the effects of estrogen might be brought about by an inhibition in the production and/or secretion of gonadotropins although a direct effect of estrogen on the tubules could not be excluded.

It is of further interest that the administration of testosterone also results in changes in the testes characterized by a decrease in size of the seminiferous tubules, sclerosis and hyalinization of the basement membrane and tunica propria, arrest of sperm formation, necrosis and sloughing of the germinal elements and atrophy or absence of the Leydig cells (11). If the testosterone is discontinued, the appearance of the tubules and the Leydig cells reverts to normal. Furthermore, the administration of testosterone results in an increase in the urinary excretion of estrogen and a fall in the urinary titer of gonadotropins (12).

Thus, in essence, pituitary destruction or the administration of estrogen or large quantities of testosterone results in a decrease in the number of Leydig cells and alterations in the tubules similar to those seen in Klinefelter's syndrome.

P. E. Smith has shown that in the hypophysectomized monkey, the administration of testosterone, if administered promptly after hypophysectomy, will result in the maintenance of considerable spermatogenesis (13). This is better demonstrated if pellets of testosterone are implanted in the testicles than if the hormone is given intramuscularly. Restoration of spermatogenesis in patients with pituitary eunochoidism has been reported to follow the use of testosterone (14). Similarly, experimentally, the use of intratesticular implants of testosterone has restored fertility in estrogen treated rats (15).

The biosynthesis of androgens and estrogens by the testis has been delineated more clearly in the past few years. It has been suggested that acetate → cholesterol → pregnenolone → progesterone → 17α-hydroxyprogesterone → 4-androstene-3,17-dione → testosterone. Androstenedione and testosterone may then be converted to estradiol 17β or estrone. It is also possible that the pathway may be via pregnenolone → 17α-hydroxypregnenolone → dehydroepiandrosterone → androstenedione → testosterone and then conversion to estrogen may ensue (16, 17).

It is of note that Slaunwhite and his co-workers have shown that the testis of a patient with Klinefelter's syndrome (XXY) was capable of synthesizing androstenedione and testosterone from progesterone and 17-hydroxyprogesterone and that testosterone can be obtained from the plasma of such patients although possibly in decreased titers (18). These observers have also shown that estrogen prevented the reduction of androstenedione to testosterone in testicular homogenates obtained from patients with cancer of the prostate but had little effect on the conversion of 17α-hydroxyprogesterone to androstenedione (17). The administration of chorionic gonadotropin concomitant with diethylstilbesterol to such patients restored the ability of the testicular homogenates to effect the reduction of androstenedione to testosterone in spite of the estrogen administration.

A possible explanation for the testicular lesion in Klinefelter's syndrome in the light of all the aforementioned observations, is that there is a primary increase in gonadotropin production which results in Leydig cell hyperplasia and increased conversion of the formed testosterone to estrogen. This results in a decreased local testicular concentration of testosterone and as a consequence

alterations in the tubular structures ensue. It is also conceivable that in some patients with this disorder the primary defect is an increase in androgen → estrogen conversion. However, in view of the efficiency of estrogen as a gonadotropin inhibitor this probably would not be compatible with the usual findings of high urinary titers of gonadotropin. The increase in estrogen locally in the testes may then decrease the conversion of androstenedione-like compounds to testosterone as the testosterone is converted to estrogen. However, it would seem possible that in Klinefelter's syndrome other defects might be present: 1) an inability of the precursors, progesterone, 17α-hydroxyprogesterone, pregnenolone or of 17α-hydroxypregnenolone to be converted into androgens by the testis, analogous to the defects seen in congenital adrenocortical hyperfunction, or 2) that weak androgens are being secreted instead of testosterone.

In regard to the first possibility, the data of Giorgi and Sommerville indicate that there is a decreased urinary titer of pregnanediol and pregnanetriol in patients with Klinefelter's syndrome (19). This would suggest that there is no defect in the conversion of at least progesterone and 17α-hydroxyprogesterone to androgen. On the other hand, Decourt and his associates believe that the anomaly in steroidogenesis in Klinefelter's syndrome may resemble that seen in congenital adrenocortical hyperplasia (20). They studied the responsiveness of patients with Klinefelter's syndrome to chorionic gonadotropin and found an inability of the testis to respond when the urinary excretions of the neutral 17-ketosteroids and phenolsteroids were employed as indices. These workers presume that in the resting state the hypertrophied Leydig cells are already responding maximally to chorionic gonadotropin. They further demonstrated that when dexamethasone is given, the urinary neutral 17-ketosteroids fell to levels as low as those ordinarily seen in women. Therefore, they suggest that the production of androgens by the testis is nil and use their findings to bolster their argument that the defect in steroidogenesis in Klinefelter's syndrome may resemble that seen in congenital adrenocortical hyperplasia. Similarly Klotz and Sors have suggested the primary defect in Klinefelter's syndrome is an inability of the Leydig cell to form androgen. Leon and his group also were able to reduce the urinary neutral 17-ketosteroids from 4.6 to 1.0 mg 24 hrs with 9α-fluorohydrocortisone but the fall observed was less if human chorionic gonadotropin was given concomitantly (21).

On the other hand, in a patient with Klinefelter's syndrome, Sturtevant and his associates were able to reduce the urinary excretion of the neutral 17-ketosteroids only by one-third through the use of 9α-fluorohydrocortisone although the corticoids were completely suppressed (22).

Our own results demonstrate that the quantities of androgen metabolites excreted in the urine of patients with Klinefelter's syndrome are within the normal range albeit frequently on the low side, and following the administration of dexamethasone significant quantities of the various fractions of the neutral 17-ketosteroids are still present in the urine. There are scant other data on partition studies of the neutral 17-ketosteroids in Klinefelter's syndrome. Johnsen found the titer of the total neutral 17-ketosteroids to be low in three

of four patients and in these the excretion of etiocholanolone was particularly reduced and that of the "rest" fraction (*i.e.*, the 11-oxygenated group) was quite low although both groups were still within the normal range (23). Ferrari and his associates reported the titer of the neutral 17-ketosteroids to be low in the two patients studied due to the decrease of 11-desoxy-17-ketosteroids in one case and to that of all fractions in the others (24). In a few previous studies, the decrease in the titer of the neutral 17-ketosteroids was found to be due in large measure to the diminution in the 11-desoxy-17-ketosteroid fraction rather than in the 11-oxy-17-ketosteroid moiety (25, 26). Indeed on the basis of such studies, Klotz and Sors suggested that the basic defect in Klinefelter's syndrome was the inability of the Leydig cells to elaborate androgen (25). Nonetheless it has long been known that the urinary excretion of neutral 17-ketosteroids varies from low to normal in patients with Klinefelter's syndrome. Giorgi and Sommerville in a study of 23 patients with Klinefelter's syndrome demonstrated the urinary titer of the neutral 17-ketosteroids to be significantly decreased from the mean obtained in normal subjects (19). The only data available on the plasma levels of testosterone are given by Slaunwhite and his associates who studied one patient and found the level to be in the low normal range (18). The data thus would indicate that there may be a decrease in androgen and or testosterone secretion by the testes in Klinefelter's syndrome in association with high gonadotropin secretion and Leydig cell hyperplasia.

It is worth examining, then, whether the defect in Klinefelter's syndrome reflects the excessive formation of estrogen from androgen in the testes. Giorgi and Sommerville report that in a group of 23 patients with Klinefelter's syndrome not only is there a significant reduction from the values encountered in normal males in regard to the neutral 17-ketosteroids, pregnanediol and pregnanetriol, but also of estrone and to a lesser extent estradiol 17-β (19). However, there was no difference in the ratio of mean urinary 17-ketosteroid to total estrogen or in the total estriol excretion. They also observed the urinary titer of estrogen to be less in patients with Klinefelter's syndrome without gynecomastia than in those with gynecomastia. Stewart and his associates, employing the Brown method, measured the titers in six subjects with Klinefelter's syndrome, four being chromatin positive and two chromatin negative patients (27). Estradiol was increased in one chromatin positive patient and estriol was decreased in two chromatin positive subjects. In our own studies, in one chromatin negative patient the total estrogen titer was markedly increased. In one chromatin positive subject the urinary excretion of estradiol and estriol were elevated. In another chromatin positive patient, the urinary estriol titer was elevated. Utilizing a biologic method, however, Vague and his co-workers found the urinary estrogen to be increased in three subjects with Klinefelter's syndrome, two being chromatin positive, the other not described (28). In other studies, increased urinary estrogen titers have been encountered but usually the levels were within the normal range (25, 26, 30). In general, then, no definitive evidence from the urinary titers can be adduced that estrogen production is increased.

No definite conclusion can be derived therefore as to the pathogenesis of the testicular lesion from the data presently available, particularly since the adrenal contributes to the urinary titer of androgen and estrogen. Studies are presently underway in our laboratory to measure the estrogen/testosterone content of the testes as well as the plasma levels in order to test the hypothesis that the defect in Klinefelter's syndrome is a primary increase in pituitary gonadotropins and a secondary increase in the testicular conversion of androgen and/or testosterone to estrogen. This theory is in contrast to the supposition that the primary defect in Klinefelter's syndrome may be a defect in androgen elaboration by the Leydig cell and that the increased secretion of gonadotropins is compensatory. In both of these theories, however, there is presumed to be a diminution in the effective secretion of testosterone from the testis. Although it has been presumed that overproduction of growth hormone induces acromegaly or gigantism, that overproduction of corticotropin results in Cushing's syndrome and overproduction of thyrotropin may result in Graves' disease, no syndrome of primary overproduction of gonadotropin has been described. Klinefelter's syndrome may represent such a disorder.

SUMMARY

Partition studies on the urinary neutral 17-ketosteroids were carried out in 9 patients, 2 chromatin negative and 7 chromatin positive, with Klinefelter's syndrome. The values obtained were in general in the lower normal range. In 6 of these subjects plus an additional chromatin negative patient estrogen assays were carried out. In one subject the total urinary estrogen titer was increased. In another, urinary estradiol and estriol, and in a third, urinary estriol were also increased. Based on findings reported in the literature as well as on these data a hypothesis is proposed that the abnormality in Klinefelter's syndrome is a primary increase in gonadotropin secretion and a decrease in testicular androgen secretion because of increased conversion to estrogen. The decrease in testicular androgen concentration results in the tubular alterations.

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ADDENDUM

In a recent publication Martin and Carden (Martin, F. I. R., and Carden, A. B. G.: Gynecomastia in Chorion-Epithelioma. Oestrogen Levels and Probable Pathogenesis. Acta endocrinol., 43: 203, 1963) reported two patients with chorionepitheliomas, gynecomastia and high urinary titers of gonadotropins and of estrogens. In the one of these subjects examined at autopsy, the testicular tubules were found to be hyalinized and prominent groups of interstitial cells were present. They concluded that the gynecomastia was produced by the action of chorionic gonadotropin on the interstitial cells of the testis. Similar results in regard to the testis histology were collected by Fine, G., Smith, R. W., and Pachter, M. R.: Primary Extragenital Choriocarcinoma in the Male Subject. Case Report and Review of the Literature. Am. J. Med., 32: 776, 1962.

The Management of Diabetes in Pregnancy

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The tenth anniversary of the establishment of an obstetrical service at The Mount Sinai Hospital occasions this review of the principles of management of diabetes in pregnancy employed in the Prenatal Diabetes Clinic.

Before the introduction of insulin, pregnancy in a diabetic patient was usually a tragic situation. Infertility in those juvenile diabetics who lived to reach childbearing age was remarkably high. When conception took place, the pregnancy frequently ended in spontaneous abortion or precipitated diabetic acidosis and coma. The relatively few diabetic women who carried pregnancy to term frequently produced either stillbirths, abnormal infants, or infants who died from undetermined causes during the neonatal period (1).

After insulin became available, the maternal mortality rate decreased rapidly from an incidence of over fifty per cent to a level comparable to that in the nondiabetic population. Juvenile diabetics who are treated with insulin now easily reach childbearing age, and are as facile in the process of conception as their nondiabetic sisters (2). Today, diabetes per se is not an indication for therapeutic abortion. Excessive fetal wastage, however, continues to plague diabetic patients. Insulin, close prenatal supervision, and early delivery have helped to reduce the forty to fifty per cent perinatal mortality rate to the present levels of fifteen to twenty per cent in offspring of mothers with pre-existing diabetes. High rates of spontaneous abortion, intrauterine and neonatal death, and congenital abnormalities persist despite modern therapy in this group of patients (3, 4), and occur to a lesser, but still significant extent in patients in whom the diagnosis of diabetes is made initially during the pregnancy (5).

PATHOPHYSIOLOGY

Carbohydrate metabolism during pregnancy is being studied with increasing intensity in an attempt to explain such phenomena as the diabetogenic effect of pregnancy and the high fetal loss in diabetic pregnancies. It can be stated with assurance that an abnormal glucose tolerance test during pregnancy is not a function of the pregnancy, but is indicative of disease, and in the vast majority of cases represents either latent or manifest diabetes (6).

Though the normalcy of the glucose tolerance test in normal pregnancy is now accepted, other defects in maternal carbohydrate metabolism during pregnancy are becoming manifest. Insulin responsiveness in the normal pregnant female is poorer than in the nonpregnant female. Clinically this manifests itself in the diabetic patient by the usually considerable increase in insulin

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requirement during pregnancy, and is certainly one of the factors for pregnancy being diabetogenic to the latent diabetic.

The fetal role in this problem has also recently come under investigation, and at least two factors seem to be involved. There is evidence that the fetus produces insulin antagonists functioning at both maternal sites and within the fetus, resulting in increasing maternal insulin needs to counteract this destruction or neutralization (7).

The placenta is the least understood of the three systems involved (mother, fetus, placenta), but there is evidence to show that it, too, does participate in responsiveness to insulin. Insulin degradation is purported to be progressively influenced by the placenta as it increases in size (8).

These physiological derangements will then manifest themselves in both the mother and the fetus. In the mother, they are represented by the increased lability of the diabetes, the increasing insulin requirement as pregnancy progresses, and the rapid and marked deterioration of diabetic control in response to complications. These derangements do not seem to have any effect on the rate of progression of any of the degenerative complications of diabetes. Indeed, microaneurysms appearing during pregnancy may disappear postpartum.

The effects of these derangements on the fetus are believed to be responsible for certain of its phenomena, such as macrosomia, increased size, and increased fat deposition.

The role of altered hormone balance in the pregnant diabetic in contributing to fetal loss has been considered for many years. Studies of pituitary and adrenal function in both the diabetic mother and her newborn do not seem to be different from the normal (9). There is evidence of increased chorionic gonadotropins and decreased estrogen and pregnanediol levels, but attempts at replacement therapy have not resulted in better survival rates than in series not so treated.

CLASSIFICATION

To standardize descriptions and facilitate evaluation of various methods of treatment, we believe it would be advantageous if physicians everywhere would adopt White's classification of maternal diabetes, as outlined below (10):

Class A: Patients with the highest chance for fetal survival, including patients in whom the diagnosis of diabetes is made on the basis of a glucose tolerance test which deviates but slightly from the normal. Such patients require no insulin and little dietary regulation.

Class B: Patients whose diabetes started in adult life at the age of twenty years or above ; those in whom the duration of the disease is less than ten years; and those who are free of vascular disease.

Class C: Patients whose diabetes is of long duration (between 10 and 19 years); those in whom the onset of diabetes occurred between the ages of 10 and 19 years; and those who have minimal vascular disease, such as retinal arteriosclerosis or calcification of the vessels of the legs alone.

Class D: Patients whose diabetes is of twenty years' duration or more; those in whom the onset of diabetes occurred before they were ten years old; and those

who have more evidence of vascular disease, such as retinitis, transitory albuminuria, or transitory hypertension.

Class E: Patients in whom calcification of the pelvic arteries is demonstrable by x-ray.

Class F: All patients with nephritis.

Prediabetes: Class A

A. Prediabetes and Pregnancy: Diabetes has always been defined in terms of an abnormality of sugar tolerance, and we have become accustomed to thinking of the disease as beginning with the onset of clinical symptomatology or with the finding of an abnormal glucose tolerance test. In recent years, however, it has become apparent that there are anatomic and metabolic aberrations peculiar to diabetes which occur long before any clinical evidence of a carbohydrate metabolic defect, and even in the presence of a normal glucose tolerance curve (11). We know, too, that the triad of retinopathy, neuropathy, and nephropathy, once considered as complications of long-standing disease, can precede any evidence of hyperglycemia or glycosuria (12). These observations have given rise to a new concept of the disease as one which begins at birth and continues for a variable period of time through a stage of occult structural and metabolic changes until an abnormal glucose tolerance curve or clinical signs and symptoms become evident. This phase which precedes overt abnormality has been variously termed subclinical, latent, or prediabetes (13). It is currently believed that the clinical or laboratory appearance of any diabetic phenomenon, albeit transient, is sufficient to alter the classification of the patient from prediabetic to diabetic.

Prediabetes can be converted into clinical diabetes by certain stress phenomena, which manifest disease may persist after the stress has abated. The priming of a patient with steroids prior to a glucose tolerance test is designed as just such a transitory stress phenomenon to convert an occult process into a temporarily manifest abnormality for diagnostic purposes (14). Steroids administered therapeutically for a variety of diseases may convert genetic susceptibility into clinical disease which remains for the duration of the patient's life, and long after steroid therapy has been discontinued. Infection, trauma, or myocardial infarction may likewise make temporarily or permanently manifest a latent diabetes. We are now aware that pregnancy acts as such a stressful situation.

W. P. U. Jackson has clearly expressed the interrelationships of diabetes and pregnancy in his many articles and editorials on the subject (15). Just as pregnancy serves as a stress phenomenon to give a prediabetic woman an overtly abnormal glucose tolerance curve, so does the prediabetes produce certain ill-defined metabolic and structural abnormalities which are hazards to a successful pregnancy. The Class A diabetic, then, is a woman with no previous knowledge of diabetes in whom the stress of pregnancy produces an abnormal glucose tolerance curve, which in most cases will revert to normal when the pregnancy is terminated but which may remain abnormal even after delivery, and in whom the prediabetic state has produced certain abnormalities which increase the fetal

and neonatal mortality of her offspring (16). By developing an abnormal glucose tolerance curve in the face of a stress phenomenon, she has demonstrated that she is a prediabetic, and that she is subject to a return of her abnormality with subsequent stressful situations, and to the eventual development of clinical disease. It is clear, therefore, that the obstetrician is in a particularly advantageous position to discover patients in whom diabetes is destined to develop.

B. Diagnosis and Case Finding: The Class A diabetic is not infrequently found if we but look for her (17, 18). In the case finding program at The Mount Sinai Hospital Prenatal Clinic, the number of Class A diabetics found each year has risen steadily, so that they now represent 54 per cent of our total diabetic series. This increase reflects the increasing diligence with which case finding has been pursued by our house staff, and is in good accord with surveys of diabetes in the population at large, which indicate that there is one unknown diabetic for every known case (19).

Every patient attending the routine prenatal clinic has her urine tested for sugar as well as albumin at each clinic visit. The introduction of Tes-Tape and Clinistix makes this test remarkably simple and practical for use by every physician. These methods are specific for glucose, and are, therefore, to be preferred over testing with Benedict's solution or Clinitest tablets, which will give a positive reaction for sugar in the benign, nondiabetic melliturias, such as pentosuria and fructosuria, and in lactosuria late in pregnancy or during lactation in the postpartum period.

Any patient who shows glycosuria is subjected to a blood sugar determination two hours after ingestion of 100 grams of glucose orally. This screening procedure is also carried out on those patients who on their initial visit give a history of 1) familial diabetes, 2) previous unexplained stillbirths, 3) large babies weighing nine pounds (4000 Gm) or more, 4) habitual abortion, 5) delivery of infants with multiple congenital anomalies, or 6) excessive obesity. We have found the two hour post 100 Gm glucose value a very satisfactory screening procedure in that it has a high degree of diagnostic accuracy and is easier for the patient, the physician, and the laboratory than a standard glucose tolerance test. The fasting blood sugar is frequently normal in early or latent diabetes, and its determination is, therefore, a very poor screening test, and should never be used for this purpose. When the results of the two hour post 100 Gm glucose blood sugar are at all doubtful, a standard glucose tolerance test is performed. If this test is normal, it is repeated every eight to ten weeks during the course of the pregnancy.

We consider a glucose tolerance test abnormal when it exceeds any of the values at two or more points on the curve, as shown in Table I. When only one point is abnormal, we repeat the test in four to eight weeks. Intravenous glucose tolerance tests are rarely necessary, and are used only when the patient is unable to tolerate the glucose by mouth. Blood sugar values in the intravenous test are the same as for the oral test, with the 15-minute, 30-minute, and one-hour values corresponding to the one-, two-, and three-hour values, respectively, of the oral test. We have recently evaluated the intravenous Tolbutamide tol-

erance test as an adjunct to the glucose tolerance test in making the diagnosis of diabetes in borderline cases, but have found it unsatisfactory for this purpose because of the frequency of false positive results in nondiabetic pregnant women (20). In the light of recent reports on the effect of thiazide diuretics on sugar tolerance in nonpregnant patients (21), we are currently studying the possible influences these drugs may have on the glucose tolerance test in the pregnant state.

Glucose tolerance during pregnancy may show even more variation than in the nonpregnant state. A normal glucose tolerance test early in pregnancy may become abnormal as the pregnancy progresses, and for this reason a single normal glucose tolerance test early in pregnancy does not rule out diabetes in a patient in whom there is good reason to suspect possible abnormality on the basis of history or findings. We have had a number of patients with a clearly abnormal glucose tolerance curve during one pregnancy who show a normal test early

TABLE I

Oral Glucose Tolerance Test-Venous Blood[1] *Upper Limits of Normal Values*

	Total Reducing Substances[2]	True Blood Sugars
	mg%	*mg%*
Fasting	120	100
1-hour	180	160
2-hour	140	120
3-hour	120	100

[1] Capillary blood values are 10 to 20 mg per 100 ml higher by any method, except for the fasting value, which is identical for all methods.

[2] Folin-Wu method.

[3] Methods of Somogyi, Nelson, Shaffer-Hartmann, and others.

in the course of a subsequent pregnancy. We have followed one patient through four pregnancies, during which she showed a normal glucose tolerance curve with a low renal threshold in the first trimester and an abnormal glucose tolerance test during the second trimester; she has required insulin during the third trimester of her last two pregnancies.

It should be pointed out that a positive test for glucose in the urine does not make a diagnosis of diabetes. Occasionally during pregnancy the renal threshold for glucose is lowered and glucose will appear in the urine at relatively low blood sugar levels (22, 23). In such cases, a glucose tolerance test will be normal. We wish to stress, however, that this lowering of renal threshold may also occur in both the known Classes B to F diabetic and the newly-discovered Class A diabetic, and this may cause some difficulty in management. Indeed, it has been our impression that a lowering of renal threshold is not as benign as was once thought, and that many of these patients with so-called renal glycosuria will develop an abnormal glucose tolerance curve during the course of the pregnancy. The case just cited is an example of this progression.

C. Management and Results: The successful management of pregnancy in a diabetic patient depends upon the close cooperation of a team including the obstetrician, internist, pediatrician, and patient. There is no substitute for frequent observation of the patient. At The Mount Sinai Hospital Prenatal Diabetes Clinic, patients are seen every two weeks until the 26th week of gestation and every week thereafter. This includes the Class A diabetic.

At the first visit a complete history is taken and a thorough physical examination performed, and routine laboratory work is scheduled. At each subsequent visit the patient is evaluated both medically and obstetrically by an internist and an obstetrician. Four fractional urines (samples taken before each meal and at bedtime) from the previous day are brought in by the patient and examined for glucose, acetone, and albumin. Weight and blood pressure are checked and the patient is examined for signs of edema or polyhydramnios. A hemoglobin determination is performed monthly. The ocular fundus is examined frequently. The degree of control of the diabetes is evaluated, and diet or medication adjusted as needed.

Aside from the frequency of prenatal visits and the timing of delivery, the majority of Class A diabetics are handled as nearly as possible as the nondiabetic pregnant patient. At the outset, no hypoglycemic medication is given; the patient is asked to eliminate sugar and all high-carbohydrate foods from her diet. In the past, she had been allowed to deliver spontaneously at term. The only exception to term delivery of the uncomplicated Class A patient was if the baby appeared to weight in excess of 4000 Gm at any time after the 36th week. In a small number of patients presenting as Class A diabetics, the abnormality in glucose tolerance becomes so great that glycosuria is persistent and the patient is often symptomatic. In recent years, we have placed such patients on Tolbutamide (Orinase) in dosages of from one to three grams daily. We have had twenty such patients in the past five years, and have had generally excellent results. In a few instances, control of the diabetes was not achieved with oral hypoglycemic therapy, and the use of insulin has been necessary in the last trimester. Patients whose diabetes is severe enough to require hypoglycemic agents for control are treated obstetrically as bona fide diabetics, and are delivered at 36 weeks (see below).

A summary of our results with this regimen is included in Table II. The combined fetal and neonatal mortality in babies of Class A diabetic mothers has been 4.4 per cent. This is considerably better than the mortality for Classes B to F pregnancies, but is still twice that of normal, nondiabetic pregnancies (24). Since many of the babies of Class A mothers have shown the same stigmata as those of the more severe diabetics, we have postulated that perhaps the same principle of early delivery which has so dramatically reduced the fetal mortality rate in Classes B to F pregnancies might be applied here in an attempt to reduce the Class A mortality to more normal levels. Accordingly, since the spring of 1962, we have attempted to deliver our Class A patients at 38 weeks, when the dangers of prematurity would not outweigh the possible benefits of early delivery. Each woman is evaluated at the 38th week as to fetal size and

suitability for induction, and if induction is feasible she is admitted for stripping of membranes, amniotomy, and or Pitocin drip. If the patient is not found suitable at 38 weeks, she is re-evaluated twice weekly until induction is possible or spontaneous labor supervenes. We have not performed cesarean section for early delivery of any Class A diabetic. It will take several years before sufficient numbers of patients are delivered under this new regimen to permit evaluation of its efficacy in reducing perinatal mortality.

D. Follow-up and Prognosis: The glucose tolerance of Class A patients returns rapidly to normal postpartum in the vast majority of cases; a glucose tolerance test should be performed on all of these women six weeks after de-

TABLE II

The Mount Sinai Hospital Prenatal Diabetes Clinic
November 1, 1952 to December 31, 1962

Total pregnancies	253	
Successful pregnancies	220	87.0%
Viable pregnancies	243	
Successful pregnancies	220	90.5%

Mortality in Viable Pregnancies

Class	Total	Stillbirths	Neonatals	% Mortality
A	137	3	3	4.4
B	59	2	2	6.8
C	24	4	2	25.0
D	19	2	2	21.0
E	1	0	0	0.0
F	3	2	1	100.0

Overall Mortality Classes A–F	9.5%
Class A Mortality	4.4%
Classes B–F Mortality	16.0%

livery, by which time it usually returns to normal. Subsequent pregnancies will very likely repeat the same cycle. The patient whose glucose tolerance does not return to normal in the postpartum period must be considered a true diabetic and managed accordingly; her classification is changed to B.

Even before the concept of prediabetes was widespread, many observers had the clinical impression that Class A diabetics whose glucose tolerance curve returned to normal were, in fact, destined to become true diabetics in the years ahead. This impression was furthered by the fact that in many elderly women in whom the diagnosis of diabetes is first made clinically, one can get a history of large babies or multiple abortions many years before. These clinical impressions, and the entire concept of prediabetes, have recently been substantiated by the work of O'Sullivan, who reports that in his group of Class A diabetics whose glucose tolerance tests returned to normal postpartum follow-up studies

ranging in time from six months to five-and-a-half years, indicate that 28 per cent of these women have developed abnormal glucose tolerance tests in the nonpregnant state, and are true diabetics (25). This figure is all the more impressive when one realizes that the majority of clinically evident diabetes develops in the older age group, and that the women in this study are all in the childbearing ages or within five years thereafter. These facts re-emphasize the importance of the obstetrician as a diabetes case-finder, and strongly bespeak his utmost cooperation in urging his Class A patients to obtain annual medical follow-up, so that recurrent abnormalities of sugar tolerance may be detected and treated at the earliest possible stage.

Manifest Diabetes: Classes B to F

A. General Considerations: As noted in the classification outline, Classes B to F patients include all those in whom diabetes was known to exist prior to pregnancy, and in whom the evidence of degenerative phenomena ranges from none to severe retinal and renal disease. Pregnancy with severe retinopathy or nephropathy, or both, will result in extremely high fetal loss, and diabetic patients in Classes E and F should be discouraged from becoming pregnant. In fact, patients in Class F, like all patients with severe renal disease regardless of etiology, do very poorly in pregnancy, and may require therapeutic abortion for preservation of maternal life. We feel, therefore, that the development of progressive retinal or vitreous hemorrhages or evidence of markedly increasing renal impairment as pregnancy progresses justifies interruption of the pregnancy; fortunately, in our experience this has never been necessary. The appearance of microaneurysms, even in great number, is not, however, an indication for interruption of pregnancy in the absence of massive retinal hemorrhages. It has been a striking experience to see many of these microaneurysms disappear postpartum, and at times even during the course of the pregnancy. In any diabetic patient, progressive degenerative changes may be accelerated during pregnancy. In our experience, the postpartum status of such patients is not markedly different from their prepregnant condition. Thus, transient maternal degenerative changes or the loss of a baby in any class except Class F does not militate against the possibility of future successful pregnancy.

B. Principles of Management: The basic principles of care include meticulous attention to hyperglycemia and glycosuria; close cooperation between the patient, obstetrician, internist, and pediatrician; hospitalization for any deviation from normal; and termination of the pregnancy at about the 36th week of gestation. These principles are in general use today in most centers caring for diabetic pregnancies. The only other feature one might consider is the use of stilbestrol and progesterone (26). When our clinic was established in 1952, we reviewed the literature on this matter and decided not to use these agents for a period of ten years. At the end of this time, our results, coupled with other studies in which hormones had been evaluated (27), led us to feel that they would have contributed little or nothing toward lowering fetal mortality.

Careful control of the diabetic state is of the utmost importance in the success-

ful outcome of pregnancy. To patients who may have been managed in the nonpregnant state on a relatively free dietary regimen, the importance of dietetic control during pregnancy is carefully explained. The need for this is due to the fact that in about two-thirds of the patients insulin requirements will progressively increase during pregnancy (28). Of the remaining third, about one-half will require little or no change in insulin dosage, and the other half may even show a decrease in the insulin dosage required, generally as a result of stricter dietary control. Any tendency to fall behind in adjusting insulin dosage upwards may eventuate in ketosis or ketoacidosis. A single bout of either may result in antepartum fetal death. It is not unusual to see insulin requirements double as pregnancy progresses. There should be no hesitancy in utilizing multiple doses of insulin, if this is required. We have successfully used Tolbutamide (Orinase) in carrying a number of pregnancies in milder diabetics to conclusion without harm to mother or child. In several instances, this drug was used until the last trimester of pregnancy, but then insulin had to be employed to achieve satisfactory control of the hyperglycemia.

In assessing diabetic control, fractional urines are usually quite satisfactory. The problem of low renal threshold in these classes is similar to that described for the Class A diabetic. In these patients, the only satisfactory means of regulation is to depend on simultaneous blood and urine sugar determinations. In the mild diabetic, as judged by insulin requirement, we feel that blood sugars should be kept very close to normal and the urines should be sugar-free. In the more severe diabetic and in the brittle juvenile diabetic, we attempt to have as little glycosuria as possible but yet avoid hypoglycemic episodes. Acetonuria without glycosuria may frequently be found. In normal nondiabetic pregnancy, the production of acetonuria secondary to minimal starvation, such as an overnight fast, is not uncommon, and this same phenomenon will be found in the diabetic. Such acetonuria is no cause for concern and need not be treated.

We do not hesitate to have the patient return several times a week if there is any deviation from normal, either clinically or chemically. Frequent communication between the obstetrician and internist, if they see the patient at different times, is essential to her welfare. At the clinic visits, the examinations and procedures are those as previously described for the Class A diabetic. Routine fundoscopic examination is important, as we have indicated above.

The patients are placed on standard diabetic diets, with supplemental vitamins and iron. If the patient is overweight or exhibits any tendency to gain excessively, she is placed on a 1500 calorie diet. Appropriate diuretic therapy is used in the presence of edema, a practice which is routine in the regular prenatal clinic.

We do not hesitate to hospitalize a patient if there is any problem. Any medical condition that may arise, whether related to pregnancy or not, must be considered a potential source of hazard and vigorously treated. A mild cystitis during pregnancy in a nondiabetic can often be cleared in 48 hours with appropriate antibiotic therapy, but in the diabetic this may be enough to precipitate ketosis and even acidosis.

C. Timing and Management of Delivery: The final step in prenatal management is determination of time of delivery. It has been our policy to terminate pregnancy 28 days before term, if all factors are favorable. The primary concern has been the size of the fetus. This has been estimated by the obstetrician mainly through palpation, and secondarily by x-ray evidence of the so-called "halo sign" and the presence of the distal femoral epiphyses. Recent work has cast doubt upon the usefulness of estimating the duration of pregnancy by the presence or absence of femoral epiphyses in the infants of diabetic mothers, and our experience would confirm this; consequently, we have not relied on x-ray assistance in recent years. We are prone to deliver a diabetic patient earlier than 28 days before term when there is evidence of advancing toxemia or excessive size of the fetus, or when previous pregnancies have resulted in intrauterine deaths before the 36th week of gestation. Delivery later in pregnancy is employed only when the fetal size is considered too small at the usual time, or in cases in which previous deliveries at 36 weeks have resulted in neonatal death.

Once having determined the time of delivery, the patient is hospitalized several days earlier to permit complete evaluation and careful control of the diabetes. Two days before delivery, the patient is changed from long acting insulin to regular insulin. The dosage is adjusted to the degree of glycosuria found in urines tested before breakfast, lunch, supper and bedtime. This will avoid hypoglycemic reactions while the patient is in labor and unable to eat. In patients treated with oral agents, these are continued to the day of delivery, and resumed if necessary postpartum.

Since 1955, we have attempted to induce labor in all Class B to E patients, primiparas included, where obstetrical indications have been favorable. If induction by successive stripping of membranes, amniotomy, and Pitocin drip is not successful within 48 hours, cesarean section under spinal anesthesia is performed. Cesarean section has been necessary in about thirty per cent of our patients. Once induction or section is started, the patient is given nothing by mouth and is maintained on a continuous intravenous infusion of ten per cent fructose. Regular insulin is continued according to a urine sample tested at least every six hours. Our results are summarized in Table II.

Following delivery, the patient is maintained on regular insulin until she is able to eat, when her usual long acting insulin is again started. The first doses are less than her usual prepregnancy dose. Supplementary regular insulin is used as needed and the dose of long acting insulin adjusted as rapidly as possible. The patient is encouraged to return to her full diet. Breast feeding presents no problem in managing the maternal diabetes.

SUMMARY

Diabetes and pregnancy are today entirely compatible conditions, but require the close cooperation and meticulous attention of both the patient and her physicians to insure the best possible outcome. In recent years, the Class A diabetic has become more widely recognized. Her offspring have a perinatal mortality considerably lower than that of the more severe diabetics, but it is

still twice that in normal pregnancy. In Classes B to E diabetes, perinatal mortality has been reduced from nearly fifty per cent to less than twenty per cent by strict adherence to the standard regimen outlined above. Further improvement must await further understanding of the pathophysiology and interrelationships of metabolic alterations in the diabetic pregnancy.

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A Case of Ileocecal Tuberculosis

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Since the advent of specific antituberculous therapy the incidence of tuberculosis has declined dramatically. Ileocecal tuberculosis has always been one of the less common manifestations of this disease, although it is well documented in the literature (1 to 9).

The case history presented here is that of a patient with intestinal tuberculosis, who was observed intermittently for a period of seven years.

CASE REPORT

O.S. (No. 43293) was first admitted to the Surgical Service at Greenpoint Hospital on April 15, 1956, when she was forty years old. At that time she complained of weakness and lassitude for ten months, attacks of colicky abdominal pain, loss of appetite and weight for four months, and the presence of a swelling in her upper abdomen for two months. There had been no vomiting, or change in bowel habit from her customary constipation of many years' duration. She had no cough or night sweats and no symptoms referable to her urinary or genital systems.

On admission the patient was undernourished and clinically anemic. Enlarged lymph nodes were present in many areas. The cardiovascular and respiratory systems were clinically normal. The abdomen was soft, not distended and no tenderness could be elicited. A soft, mobile mass of variable size was felt in the epigastrium. There were no other palpable abnormalities.

A clinical diagnosis of intermittent, incomplete intestinal obstruction was made, confirmed by increased tenseness of the epigastric mass during attacks of pain. Barium enema examination showed dilated loops of bowel which were interpreted at that time as colon. Chest x-ray showed several small areas of calcification, but there was no evidence of active tuberculosis or other recent disease.

A lymph node biopsy was performed on April 26, 1956. Microscopy showed "hyperplastic lymphadenitis," and no further conclusions were drawn.

Exploration was advised for persistent colicky pain and vomiting and to determine the nature of the upper abdominal mass.

At laparotomy on May 14, 1956, many enlarged, matted, yellowish lymph nodes were found in the mesentery of the small intestine. At the beginning of the ileum there were in close proximity, two areas of marked small bowel stenosis with proximal dilatation of the intestine. Four similar lesions were encountered in the distal ileum. The other organs were normal. Two segmental ileal resections were performed, continuity being restored by two separate end-to-end anastomoses.

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The patient's postoperative recovery was uneventful and she was discharged from the hospital in satisfactory general condition on May 30, 1956.

The gross and microscopic diagnosis of the surgical specimen was ulcerocaseating tuberculosis, circumferential stenosing ulcers being present at the strictured areas of small bowel, and caseation in the lymph nodes. No tubercle bacilli were found then, or at a more recent re-evaluation of these specimens. With this pathological diagnosis established, sputa were examined for tubercle bacilli. Several specimens showed no tubercle bacilli on smear or subsequent culture. Streptomycin and penicillin had been given to cover the postoperative period, but no antibiotic treatment was continued. Arrangements were made for the patient to go to a sanitarium, but were not taken up by the patient.

Subsequent to her operation the patient attended the Surgical Clinic sporadically. On January 15, 1957, she was again admitted to Greenpoint Hospital for repair of an umbilical and scar hernia. At that time only minimal symptoms were present apart from some pain in the hernia. An intraperitoneal biopsy taken at that operation showed tuberculous lymphadenitis, but no further specific treatment was advised.

During the next four years, the patient attended Greenpoint Hospital intermittently with complaints of abdominal pain, but there is no record of further definitive investigations, and only symptomatic treatment was given. During this period the patient had two additional pregnancies. Her eleventh pregnancy resulted in mild toxemia with delivery of a stillborn baby in May 1958. She was again admitted in labor in 1959, giving birth to her twelfth child by normal spontaneous delivery on April 1, 1959.

In 1962, symptoms again became more severe, leading to the most recent admission to the Surgical Service at Greenpoint Hospital on December 2, 1962. The patient complained of intermittent attacks of colicky pain in the right lower quadrant of her abdomen for four months, frequently accompanied by vomiting. Complete obstruction had never occurred, and the attacks had always resolved spontaneously on a self-imposed regimen of bed rest and fluid diet. During this period the patient lost her appetite and grew thinner. There had been no cough, night sweats or other relevant complaints. The bowels had remained constipated as before.

On inquiry into her personal history, it was found that the patient was born in Puerto Rico but lived in the United States since early adulthood. Prior to leaving her native country she had lived in a rural community, but was not aware of having drunk unpasteurized milk, or ever having a cough, sputum, or other significant disease in her childhood. There was no family history of tuberculosis.

Physical examination on this admission showed evidence of recent weight loss, clinical anemia, and generalized slight to moderate lymph node enlargement. The cardiovascular and respiratory systems were clinically normal. The abdomen was moderately distended and tympanitic. A large, firm mass was felt in the right iliac fossa. The mass was tender and slightly mobile. No other abnormalities were evident. In view of these findings, a diagnosis of recurrent tuberculous intestinal infection was made.

Laboratory findings included a hemoglobin of 8 Gm%, a sedimentation rate of 60 mm in one hour, and a normal white cell count. Many specimens of gastric washings, 24-hour urine, stool, and one of menstrual flow showed no tubercle bacilli on direct smear, culture or guinea pig inoculation. Chest x-ray was unchanged since 1956, showing several small areas of calcification only. There was no evidence of active tuberculosis or other disease. Barium studies revealed a normal esophagus, stomach and duodenum. The terminal ileum showed marked dilatation, and persistent irregular narrowing of the cecum and proximal ascending colon was demonstrated. A soft tissue mass was present around the cecum. Many calcified lymph nodes were seen on both sides of the abdomen. Although bacteriological proof had not been obtained, the investigations confirmed the clinical diagnosis of ileocecal tuberculosis. It was decided that preliminary specific antituberculous therapy should be given for four to six weeks, to be followed by surgical removal of the affected intestine. Treatment with streptomycin, 1 Gm, INH 100 mg t.i.d., and PAS, 4 Gm t.i.d. commenced on December 18, 1962, according to this plan. During the subsequent two weeks, the patient had two attacks of virtually complete intestinal obstruction, manifested by colicky abdominal pain, distention, and vomiting. Although both episodes responded satisfactorily to treatment with nasogastric suction, it was felt that surgical intervention should not be delayed further, for fear of developing irreversible obstruction, and its complications.

At laparotomy on January 7, 1963, a large mass was found in the right iliac fossa, consisting of swollen and adherent terminal ileum and cecum, the ileum proximal to the lesion being moderately distended. The two previously performed small bowel anastomoses were both satisfactory and showed no narrowing. Numerous enlarged, matted, calcified lymph nodes were found in the mesentery of the small bowel and in the retroperitoneal tissues of both sides of the abdomen. The remainder of the abdominal cavity and its contents were of normal appearance. A right hemicolectomy was performed, removing all the diseased small and large bowel. Continuity was restored by end-to-end ileotransverse colostomy.

The patient's subsequent course was entirely uneventful. Oral feeding was resumed on the third postoperative day and normal diet was rapidly taken thereafter, accompanied by return of normal bowel movements. Intramuscular streptomycin was continued throughout this period, and oral antituberculous therapy was reintroduced with the resumption of oral feeding. The patient was discharged from Greenpoint Hospital in satisfactory general condition on the 14th postoperative day, continuing her triple antibiotic therapy.

PATHOLOGY

The ileum excised at operation was somewhat dilated and thickened, but showed no ulceration or stricture. The ileocecal valve was completely destroyed. The mucosa of the cecum showed a large, flat ulcer on its posterior surface, 10 cm in length, where the wall of the intestine had been almost completely destroyed. There was moderate thickening and fibrosis of the remaining portion of the cecum and proximal ascending colon, this being most marked in the

vicinity of the ulcerated areas. Numerous calcified lymph nodes, some containing central caseation, were also present in the specimen.

Microscopically, the diseased areas showed chronic tuberculous granulomata with areas of caseation in many nodes and some calcification. No tubercle bacilli could be demonstrated with special stains on smears or culture from the bowel or lymph nodes.

The patient has been seen on several occasions in the Outpatient Clinic. She has remained well clinically, free of symptoms and is continuing with her antituberculous treatment.

DISCUSSION

At the time of this patient's operation in 1956, she had tuberculous ulcers and strictures of the small intestine and caseation of the mesenteric lymph nodes. No tubercle bacilli were found in her sputum and a chest x-ray showed scars of old tuberculosis but no signs of active disease. The pulmonary infection had clearly healed or become quiescent by 1956. It may be assumed that intestinal infection had occurred previously through swallowing infected sputum. The ulcerating variety of intestinal infection is generally accepted to be secondary (1), although our patient had no recollection of any periods of lung disease which could account for such a process. Since she lived in a rural area, it is possible that the intestinal infection was due to drinking infected milk. That this is the mechanism in many cases is confirmed by Crohn and Yarnis who found an incidence of 10 to 25 per cent of bovine tubercle bacillus in such cases, in reviewing various series (8). The disease leading to the second resection in 1962 was almost certainly a continuation of the original process. Lymph nodes were known to be affected by tuberculosis in 1956, and again in 1957 when a biopsy was taken at the time of the umbilical hernia repair. It is remarkable that this patient continued to lead a fairly normal life in the intervening years, and had two additional pregnancies. The case presented here, therefore, should be considered as one of secondary intestinal tuberculosis.

The rarity of true primary ileocecal tuberculosis is confirmed by the work of Crohn and Yarnis, who found eight cases only in reviewing 4,800 autopsies and all the surgical specimens for the years 1926 to 1938 at The Mount Sinai Hospital (8). In a number of other reports, this distinction is not stressed, and as most of the cases examined had active or known pulmonary tuberculosis, their intestinal infections were secondary to lung disease (4, 5, 7).

The accuracy of the diagnosis in our patient may be questioned as it was not possible to demonstrate the tubercle bacillus histologically or by culture. The highest incidence of positive cultures found in the available literature was in a report from India (1). These investigators were able to show 14 positive cultures in 37 specimens removed at operation. Direct examination for tubercle bacilli in their specimens, however, also produced a very low yield, and this paper implies that a high percentage of their patients had active pulmonary tuberculosis. Hoon, Dockerty, and Pemberton were able to demonstrate tubercle bacilli in 33 per cent of 58 cases (2). But their series was a review of cases from 1921 to 1946, and makes this virtually a pre-antibiotics series, so that the

likelihood of such positive findings was far greater than it would be at present. Their report accepts the presence of "characteristic caseation in tubercles in involved bowel or lymph nodes" as adequate evidence of tuberculosis. Similarly, Paustian and Bockus (1) accept typical gross and histological appearances as adequate criteria for this diagnosis, although both groups of authors look for additional proof in direct microscopy and culture of the specimen. In the eight cases of primary ileocecal tuberculosis described by Crohn and Yarnis, tubercle bacilli were seen on direct examination of one case only, and none were positive on culture or animal inoculation (8).

Our patient showed the typical gross features and histology of tuberculosis on three occasions (1956, 1957 and 1962) and this diagnosis is entirely acceptable.

The treatment of ileocecal tuberculosis is both medical and surgical (1). As in all other forms of tuberculosis, the introduction of specific antituberculous agents has revolutionized the management of this disease, as it achieves arrest of destructive processes and allows healing to take place. In organs with a large reserve, such as the lungs or the kidneys, localized loss of normal tissue due to scarring usually imposes no great strain on the functional capacity of the system, and surgery has little part to play if the disease is truly quiescent. When hollow, tubular viscera are affected, healing with fibrosis is always likely to lead to obstruction, and this is well exemplified in tuberculosis of the intestines. Surgery may be required to relieve the complications of healing by scar tissue.

In this case, resection of the lesion was necessitated by the recurrent episodes of obstruction, and the fear that these would no longer respond to intestinal decompression. Prevention of the complications of abscess, perforation, or fistula could similarly be achieved only by an operation. Although antibiotic treatment will make it possible to avoid surgery in some patients, it is of almost greater importance in providing a far wider margin of safety for those patients who will still require resection for the local complications of this disease.

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Haptoglobinuria in Renal Disease

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In 1938, Jayle and Polonovski demonstrated the existence in human serum of a hemoglobin binding alpha-2-mucoprotein which they subsequently called haptoglobin (1, 2). More recently the urine of nephrotic as well as normal individuals has been shown to contain Hp 1-1 and Hp 2-1 (3 to 6). Although under the conditions of high urinary protein loss, haptoglobin of the remaining common genetic type and higher molecular weight is detectable in urine, its presence has not been reported formally until this communication.

MATERIALS AND METHODS

Six patients with proteinuria secondary to chronic renal disease were selected to represent the three most common haptoglobin phenotypes. Twenty-four hour urine specimens containing 0.1% phenol as preservative were centrifuged and concentrated to a 7 to 10% protein concentration by dialysis against 30% polyvinylpyrrolidone. Total urinary protein was determined by the biuret method and urinary haptoglobin by the method of Connell and Smithies (7). Hemoglobin binding was demonstrated for the urinary haptoglobin by starch gel electrophoresis. Serum specimens obtained on the same day were similarly examined for protein and haptoglobin. Haptoglobin typing was performed by starch gel electrophoresis according to the technique of Smithies (8). The results obtained are presented in Table I.

TABLE I

Case	Hp Type	Serum Hp (mg %)	Urine* Volume (ml)	Urine* Protein (mg)	Urine* Hp (mg)
A	1-1	280	1,100	2,340	14.8
B	2-1	228	1,200	4,200	10.1
C	2-1	72	700	1,230	23.7
D	2-1	114	700	2,484	28.5
E	2-2	180	860	656	2.2
F	2-2	110	1,500	1,270	2.9

* 24-hr specimen

DISCUSSION

Phenotypically unchanged haptoglobin of all the common genetic types has now been demonstrated in the urine of patients with proteinuria. It may be in-

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ferred that the previous inability to demonstrate Hp 2-2 in normal urine in particular, relates to its greater molecular size (5, 6). With the techniques of the present study however, no relationship between the molecular size of the haptoglobin polymer and the degree of haptoglobinuria or of proteinuria could be established from the examination of a small group of patients with widely disparate renal function.

SUMMARY

Urinary haptoglobin of identifiable phenotype can be demonstrated in patients with chronic renal disease having Hp 2-2 as well as Hp 1-1 and Hp 2-1 phenotypes.

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Supine Hypotensive Syndrome, Spinal Anaesthesia, and Apparent Cardiac Arrest. A Case Report

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INTRODUCTION

The supine hypotensive syndrome, a condition peculiar to the latter part of pregnancy, has been clearly documented in the medical literature in the past decade (1 to 12). The consequences of the combination of the supine hypotensive syndrome and the vasomotor effect of spinal anaesthesia has been noted in early reports (6, 13) and it has been suggested that the tragedy of sudden death from spinal anaesthesia at Caesarean section encountered during the early part of this century may have arisen from their combination (13, 14). The following case presentation is illustrative of the consequences which may follow spinal anaesthesia in a patient experiencing the supine hypotensive syndrome.

CASE REPORT

E.C., a 31 year old Puerto Rican primigravida whose expected date of confinement was November 21, 1962, was admitted to The Mount Sinai Hospital Obstetrical Service at 4:24 A.M. on October 27, 1962, complaining of lower abdominal pain of about two hours' duration. Her prenatal course had been unremarkable. Clinical pelvimetry suggested borderline disproportion but x-ray pelvimetry revealed the pelvis to be within normal limits. On admission, examination revealed a term sized infant with the patient in prodromal labor; she was observed on the antepartum ward for about twelve hours. The patient then began spontaneous labor which was desultory. After six hours, the vertex was snuggly over the pelvic inlet at station minus two, the cervix was completely effaced and six centimeters dilated, and there was a small bag of forewaters. A solution of 5% glucose and water with 5 minims of syntocinon in 500 cc was started slowly intravenously and the membranes were ruptured, releasing a small amount of clear amniotic fluid. After two hours of good labor, the station of the vertex was unchanged, and the cervix was three cm dilated and thick. The fetal heart had remained good and the patient's blood pressure was sustained at 110/70. At no time did she complain of dizziness, faintness, or nausea. The oxytocic was discontinued and the patient was readied for Caesarean section, the indication being cephalopelvic disproportion. At 1:45 A.M. on October 28, 1962, the patient was in the operating room prepared for anaesthesia. The patient had received promazine (Sparine®) 50 mg intramuscularly about eight hours prior to operation. At this time she received meperidine (Demerol®) 75 mg and scopolamine 0.4 mg intravenously. About four hours before operation, the patient was given meperidine 50 mg and scopolamine 0.3 mg intravenously.

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In the operating room, the patient was prepared for spinal anaesthesia; her blood pressure was measured at 120/80 in the supine position and her pulse was 82. Methoxamine (Vasoxyl®) 5 mg was administered intramuscularly before lumbar puncture. In the sitting position, a lumbar puncture was performed with a ⅝22 gauge needle in the L3–L4 interspace, and seven mg of 0.3% tetracaine (Pontocaine®) was injected into the subarachnoid space. Blood pressure readings taken immediately thereafter indicated a decline from 100/70 to 90/60. With lateral uterine displacement the blood pressure rose to 100/60 for about 15 seconds and then fell to 70/0. Methoxamine four mg was given intravenously but no blood pressure was obtainable. The patient was noted to be cyanotic and apneic; femoral and radial pulses were not palpable. Auscultation over the precordium by two physicians failed to reveal an audible heartbeat.

Simultaneously, breathing was controlled by means of closed circuit forced respirations, closed chest cardiac massage was begun and a lower segment Caesarean section was performed. A living 4250 gram male infant in fair condition was delivered approximately three minutes after development of profound hypotension. There was no observable bleeding from the tissue on entering the peritoneal cavity, and dark, red blood welled up out of the uterus after the placenta had been removed. There were no palpable pulsations in the abdominal aorta immediately after delivery. After one or two minutes of clinical asystole, a regular apical beat returned. An attempt was then made to intubate the patient, and during the procedure she regurgitated coffee ground material. Although most of the vomitus was suctioned out of the mouth and pharynx, it was felt that a small amount might have been pushed into the respiratory tract. The endotracheal intubation was accomplished under direct vision.

The uterus was then closed in two layers and the abdomen was closed in layers, a seton drain being left subcutaneously. Before the uterus was closed, the patient began to breathe spontaneously. No vasopressor agents were used postpartum.

Immediately postpartum, a neurological examination revealed bilateral Babinski, Chaddock, and Hoffmann signs, ankle and patellar clonus, and reaction only to pin prick, all of which was interpreted as representing diffuse cerebral dysfunction secondary to transient cerebral ischemia. An ECG immediately postpartum was within normal limits. Neurological status improved rapidly, and 15 hours postpartum neurological re-evaluation was within normal limits. Urine output was good and bleeding was minimal. Six hours postpartum the patient developed a tachycardia of 140 beats per minute, and sticky rales were heard over the right base. A diagnosis of aspiration pneumonitis was made, sputum for culture was obtained, and broad spectrum antibiotics were begun. The tachycardia persisted for 48 hours. A chest film showed some increased vascular markings in the right hilar region. An ECG taken 48 hours postoperatively suggested subendocardial ischemia. The patient ran a low grade fever for 48 hours and then responded well to supportive therapy. Sputum culture was reported as Staphylococcus aureus, coagulase and hemolytic positive. Antibiotics were discontinued after five days and a chest film on discharge showed platelike

atelectasis in the right lower lobe. The patient was subsequently seen two and six weeks postpartum and made an uneventful recovery.

The infant developed convulsions about eight hours after birth, became extremely tachypneic, and was placed on anticonvulsant therapy. After two days of respiratory embarrassment, the infant began to feed and react normally. At the six week check-up it had grown and developed normally.

DISCUSSION

The diagnosis of the supine hypotensive syndrome was made following the patient's blood pressure response to lateral uterine displacement soon after being placed in the supine position. This phenomenon has been observed previously (2, 5, 6, 7, 9, 10). The response was only fleeting however, as the induced vasomotor relaxation of the spinal anaesthesia supervened. Although the diagnosis of the supine hypotensive syndrome may be striking in the antepartal period, there are times when it may be of such a degree as to be clinically inapparent (14); vascular collapse may then be precipitated by an agent which tends to lower the blood pressure, such as spinal anaesthesia (9, 16). It is postulated that a considerable amount of blood is pooled in the lower extremities and is trapped there by the blockade of the inferior vena cava by the gravid uterus (4, 7, 8, 17, 18). This blockade has been considered mechanical (4, 5, 7, 8), although a neurogenic mechanism has been suggested (1, 15, 18, 19). The treatment of choice is rapid emptying of the uterus (2, 6, 9). The rationale of this therapy is explained by the return of the sequestered blood in the lower half of the body to the circulation, and the re-establishment of blood pressure (18). When vaginal delivery is anticipated, the hypotension that develops either before or after spinal anaesthesia may be treated by turning the patient on her side (1, 6, 7, 9). When Caesarean section is going to be performed, and hypotension develops before anaesthesia, a change to the lateral position may improve blood pressure levels (2, 6, 15). When spinal anaesthesia is being used in patients undergoing Caesarean section and hypotension develops soon after it has been placed, immediate delivery will alleviate the condition (2). When the diagnosis is not made two other conditions are considered: a ruptured uterus or a high subarachnoid block (20). Treatment for the former condition may result in an unnecessary laparotomy (5). Treatment for the latter will be unsuccessful, as the use of vasopressor agents will be ineffectual (9).

This patient was considered to have a cardiac arrest since all objective parameters available for measuring cardiac activity showed no function. It is postulated that when the venous return to the right auricle was significantly compromised, cardiac output dropped, and profound hypotension developed (14, 18).

By observing all the routine precautions attendant to surgery, that is, full preparation for endotracheal intubation, functioning intravenous infusion, careful monitoring of vital signs, and adequate medical and nursing staff, the management of the emergency was carried out in an organized systematic fashion. The value of this regimen was clear.

COMMENT

The sudden inexplicable death of patients who are undergoing Caesarean section, after receiving spinal anaesthesia, has been explained on the basis of unusual susceptibility of pregnant patients to spinal anaesthesia. Supposedly, this was a result of a special susceptibility of the bulbar centers to drugs, an alteration in the hydrodynamics of cerebrospinal fluid, or the raising of the anaesthetic level by sustained intra-abdominal pressure of labor (14). Several authors have observed that the combination of the supine hypotensive syndrome and spinal anaesthesia may have been responsible for these sudden fatalities (13, 14, 20). The pattern of these cases is characterized by sudden death some minutes after the patient had been given spinal anaesthesia and had been placed in the supine position, failure of the appreciation of the insidious onset of circulatory collapse, and ineffectual methods of resuscitation because of failure to make the proper diagnosis (14). The patient herein presented would have fallen into this pattern had it not been for the early diagnosis and subsequent management.

SUMMARY

A case illustrating the effect of spinal anaesthesia on the supine hypotensive syndrome is presented.

Rapid emptying of the uterus enabled re-establishment of cardiac function and blood pressure.

Support is given to the postulate that the combination of spinal anaesthesia and the supine hypotensive syndrome may have been responsible for unexplained fatalities at Caesarean section during the early part of this century.

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Neurological Management of Congenital Malformations of the Brain Stem and Upper Cervical Spinal Cord

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Congenital malformations of the contents of the posterior cranial fossa occur infrequently. Their clinical manifestations usually appear during the first decade, but can occur in late adult life. The most common type is the Arnold-Chiari malformation. Often, the diagnosis is suspected because of associated bony abnormalities, *i.e.*, platybasis or basilar impression. However, 21 cases of Arnold-Chiari malformation unassociated with bony abnormalities of the skull were found in the literature. Only four of these cases were diagnosed prior to surgery (1 to 7). The purpose of this paper is to present three somewhat similar cases and the diagnostic problems they posed.

CASE REPORTS

Case 1. Ten months prior to admission, a 62 year old woman noted the onset of pain in the right shoulder and right occiput, associated with numbness in the fingers of the right hand. Minimal weakness of the right upper extremity was also reported. Four months later, she complained of weakness of both legs. Neurological examination showed no abnormality of the mental status or cranial nerves. Her gait seemed normal, but there was weakness of the lower extremities during tapping and pivoting, most marked on the right. In addition, she had weakness of abduction and adduction at the right shoulder, and of extension and flexion at the elbow. The right biceps tendon reflex was depressed. There were no pathological reflexes. There was hypalgesia on the right side below C-2. Appreciation of vibration was absent below the knees bilaterally. Skull x-rays showed no abnormality, but there was a minimal degree of osteophytosis of the cervical vertebrae. On lumbar puncture, there was a slight delay of pressure rise on the Queckenstedt maneuver with the neck extended. Cerebrospinal fluid cell count and protein were normal. A cervical myelogram revealed a smooth, cupped block at the C-1 to C-2 level. A tentative diagnosis of foramen magnum tumor was followed by surgery. An Arnold-Chiari malformation was found. There was progressive improvement following a decompression procedure.

This case illustrates three major points: first, cervical root and cord symptoms may be produced by such a malformation; second, age alone does not rule out such a possible diagnosis; third, careful myelography must include visualization of the foramen magnum (at this time, the pantopaque media is carried up to the clivus on all patients with cervical pathology). In retrospect, following more experience with this technique, the myelogram was suggestive of the correct diagnosis, *i.e.*, herniated cerebellar tonsils.

Case 2. A twenty year old woman was referred for neurological evaluation because of persistent obesity and a deformed right hand. However, she also related that since 1952, she had occasional episodes of numbness, with pins and needles sensations, first involving the right hand, then the forearm, face and the right side of the tongue. The entire attack usually lasted about five minutes, without loss of consciousness. There was some slurring of speech.

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In addition, she had daily hot and cold flushes, associated with dizziness. These spells had recurred since 1955 and, on two occasions, the patient lost consciousness for an unknown period of time (approximately "a few minutes") and suffered minor injury. Since 1955, she walked as if drunk. Perspiration on the right side of the face and tearing in the right eye were said to be more prominent. In 1957, there began a progressive deformity of the left hand. Her vision became impaired and, at times, objects seemed to glow and were not clear unless held close. In the three to four months prior to admission, there were two or three transient periods of double vision.

At the time of examination, the woman was alert, with an intact mental status. As a college senior, her I.Q. was purported to be 158. There was subjective horizontal diplopia on left lateral gaze without evident oculomotor paresis. Rotatory counterclockwise nystagmus was noted on direct forward gaze, right and left lateral gaze, and on downward gaze, but not on upward gaze. Both corneal reflexes were depressed and there was diminished pin sensation in the region supplied by the ophthalmic division of the right trigeminal nerve. There was a moderate degree of atrophy of the left side of the tongue. Motor examination revealed a dystaxic gait and a positive Romberg sign. The left hand and arm were weak, with atrophy of the intrinsic hand muscles, producing a claw-like deformity. Myoclonic movements were noted in the left upper extremity. Muscle tone was normal. Finger-nose and heel-knee performances were normal. Deep tendon reflexes were diminished in the upper extremities, but hyperactive in the lowers, with bilateral ankle clonus. The plantar response was flexor bilaterally. The sensory examination was normal.

The multiplicity of symptoms and signs seemed to involve the cerebrum, brain stem, and cervical cord or roots. The electroencephalogram was abnormal. X-rays of the skull and cervical spine revealed only narrowing of the intervertebral space between C-5 and C-6, with osteophyte formation at that level. A lumbar puncture was normal, except for a slight elevation of protein to 61 mg%. Pneumoencephalography demonstrated massive dilatation of the lateral ventricles, third ventricle and anterior portion of the fourth ventricle. The posterior portion of the fourth ventricle was not well seen. Because of this inadequacy, a myeloencephalogram was performed. This was initially interpreted as normal, but abnormal in retrospect, after further experience in interpreting such x-rays.

Following the above procedures, the patient's condition remained stable, except for complaints of back and neck pain. Six days later, she suddenly became quadriplegic and virtually blind within a two-hour period. The severity of the condition fluctuated hourly, with periods of partial recovery. Nevertheless, a tracheotomy was required because of respiratory distress and an emergency craniotomy was performed. At surgery, a marked increase in the cerebrospinal pressure was found. The first cervical vertebra was mobile and partially subluxated. There was a thick fibrous band at the posterior portion of the foramen magnum compressing the spinal cord. The cerebellar tonsils were herniated and covered with a thick gray membrane, which was incised in order to reach the fourth ventricle. A suboccipital decompression and removal of the arch of the atlas was performed.

There was slow improvement following surgery, with return of vision and power in the upper extremities. Sensation was defective below T-8. Three months later, upon transfer to a rehabilitation center, she still had a paraparesis, the thoracic sensory level and a diffusely abnormal EEG. However, readmission to The Mount Sinai Hospital was required three weeks hence, because of spells of unconsciousness and bulging of the decompression site. Lumbar puncture revealed a pressure of 600. Before further therapy could be attempted, she expired.

This case demonstrates how a congenital brain anomaly at the base of the skull can cause, over many years, marked structural changes with only a paucity of symptoms. It seems that the band of connective tissue slowly closed off the foramina of Magendie and Luschka. As a result, tremendous internal hydrocephalus developed, but so slowly that intellectual function was not significantly

impaired. It is amazing, considering the size of the ventricles, that she was a bright college student. The dilation of the third ventricle is evidence of damage to thalamic and hypothalamic tissue. One can only guess that this may have caused the obesity. The atrophy of tongue and hand can be explained by a hydromyelia of the central canal. Again, myeloencephalography provided good visualization of the foramen magnum area and posterior fossa contents.

Case 3. A twenty year old man was admitted to the hospital with a history of double vision in the horizontal plane for three years. Fatigue seemed to increase the visual difficulty. Two years prior to admission, he began to bump into people and objects because of a staggering gait. In addition, he complained of difficulty in handling objects with the right hand. He could no longer excel in his mechanical drawing classes. However, his grades remained consistently high. A neurologist examined him and found, in addition to the oculomotor and motor system dysfunction, diminished position sense in the fingers of the right hand and dullness to pin on the right side of the face. He was hospitalized elsewhere. A pneumoencephalogram was unsuccessful, but a ventriculogram was performed and was reported to be normal.

It was thought that the patient was suffering from either a type of demyelinating disease or a slow growing medullary neoplasm. Conservative management was advocated. Because of continued progression of gait disturbance, dystaxia and incipient right hemiparesis, he was hospitalized for further study.

General physical examination revealed him to be obese, with little facial or axillary hair and mild gynecomastia. The mental status was intact. There was slight limitation of abduction of the right eye. Counterclockwise rotatory nystagmus was observed on right and left lateral and on downward, but not upward gaze. His gait was quite ataxic, with the patient falling to the right. There was marked weakness of the right arm, most severely in the hand muscles. Finger-nose and heel-knee tests were postive bilaterally. The deep tendon reflexes were hyperactive on the right, with ankle and wrist clonus. A Babinski sign was found on the right. Sensory examination was normal, except that vibration sensation was impaired below D-4.

Lumbar puncture revealed a protein of 74 mg%, with normal manometric pressure and cell count. The x-rays of the skull and cervical spine were normal. A pneumoencephalogram showed no ventricular filling. A myeloencephalogram demonstrated a filling defect at and below the foramen magnum, suggestive of tonsillar herniation. There was also questionable bowing of the aqueduct of Sylvius.

A subsequent suboccipital craniotomy and cervical laminectomy confirmed the possible preoperative diagnosis of congenital abnormality in the region of the foramen magnum. Following surgery, the patient did well, but his functional defect remained incapacitating.

Again, the difficulty in diagnosis is apparent (not until the myeloencephalogram was the possibility of a congenital defect given much thought) and again, the value of this procedure was demonstrated. There had been a suggestion that radiotherapy be given because the ventriculogram was normal and an intrinsic medullary lesion was hypothesized. An important point is that radiotherapy should not be given until a lesion is demonstrated. It is preferable to wait and repeat a diagnostic procedure, especially when, at this time, we have added to our clinical armamentarium techniques which obviate the need for surgical diagnostic procedures.

SUMMARY AND CONCLUSIONS

Twenty-one cases of Arnold-Chiari malformation in adults, in the absence of bony abnormalities, were found in the literature. In four only was a preoperative

diagnosis made. Three case histories were presented. The first was a 62 year old woman with signs and symptoms of cervical cord and root disease, and a pantopaque block in the upper cervical region. The second case was a twenty year old woman, with evidence of cerebral, brain stem and cervical spinal cord disease. Herniation of the cerebellar tonsils could be demonstrated by myeloencephalography. The third case was a twenty year old man suspected of having a slowly growing posterior fossa neoplasm. Again, myeloencephalogram showed tonsillar herniation.

It is concluded that in patients with progressive neurological disease localized to the lower brain stem-upper cervical cord, regardless of age and absence of bony abnormalities of skull and vertebrae, congenital brain and spinal cord pathology should be considered and can be diagnosed, especially by utilizing the technique of myeloencephalography.

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The Differential Diagnosis of Pancreaticoduodenal Biliary Obstruction

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Since the important surgical advances introduced by Whipple, who in 1935 (1) established the anatomic and surgical principles of resection of pancreatic-biliary carcinoma, the differential diagnosis of extrahepatic biliary tract obstruction has assumed increasing clinical importance. In addition to differentiating obstruction due to calculus, stricture or malignant invasion, less common parasitic or congenital lesions and primary infective cholangitis must be considered (2).

An accurate diagnosis may alter critically the surgical decision to explore promptly or not and may certainly affect the choice of procedure. The diagnosis of extrahepatic biliary obstruction is regarded frequently as sufficient indication for exploration, and further attempts at diagnosis considered redundant as it is felt that decisions concerning diagnosis and therapy can be made at exploration. That this is not true is borne out when the surgeon is faced with the complications of acute infection, fibrosis and old adhesions, superimposed on pancreatic inflammation; the surgical differential diagnosis in such cases is extremely difficult, even with the gross pathology at hand. The delay incurred in preliminary mobilization and dissection to establish diagnosis or the necessity for cutting across a field of tumor while making an operating room diagnosis may also delay or hinder appropriate surgical therapy. The frequent difficulty of making a definitive frozen section or needle biopsy diagnosis further complicates the problem.

It is increasingly well recognized that the presence of a common duct stone does not exclude the presence of tumor or stricture of the more distal bile ducts. Even when a correct diagnosis of obstructive early malignancy is established in the operating room, the preoperative preparation essential for a successful en-bloc resection is often different from that necessary for the removal of a stone. The lack of adequate preparation may necessitate a staged procedure, which might have been avoided, or alternately result in failure to achieve a radical cure.

The application of the techniques of duodenal cytology, duodenal drainage and response to secretin may considerably narrow the diagnostic probabilities. Repeated and more refined radiographic methods may establish a likely diagnosis and careful bacteriologic techniques avoid overwhelming postoperative infection.

The following cases illustrate the problems of differential diagnosis prior to surgery in the clinical course of extrahepatic biliary obstruction. They emphasize

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the need for reliance on precise diagnostic methods to help eliminate a frequent contributory cause of death, namely error in diagnosis.

CASE REPORTS

Case 1. Benign Ulcerated Vaterian Stricture Simulating Malignancy

A 74 year old white woman (116161) was troubled by recurrent bouts of bimonthly acute abdominal pain radiating to the back and right subscapular region and associated with febrile episodes, moderate jaundice, choluria and acholic stools. These attacks followed a cholecystectomy for gall stones eight years prior to this admission.

The patient was well developed and well nourished with a xanthoma of one eyelid. She presented two fingersbreadth hepatomegaly and cardiographic findings of an old diaphragmatic infarct without recent activity. A differential blood count was within normal limits. Laboratory findings were an SGOT of 63; albumin 3.4 Gm%; globulin 3.4 Gm%; thymol turbidity 2.2 units; prothrombin time 13.5/12; bilirubin 1.6/0.3 mg%; alkaline phosphatase 20–30 King-Armstrong units. On four separate occasions the stool was guaiac negative. Urinalysis showed a trace of bile and no urobilinogen.

A clinical diagnosis of common duct stone was made and exploration revealed a markedly dilated common duct with a 2.5 cm stone impacted at the lower end. This was removed and a № 9 Bakes dilator was passed into the duodenum.

T-tube cholangiograms taken in the operating room eight days postoperatively, however, demonstrated a 1.5 cm ulceration in the medial wall of the distal common duct. A pancreatic secretion test showed normal bicarbonate levels with a somewhat low volume. One of three cytology studies on the duodenal aspirate was reported showing atypical cells compatible with a malignancy. On this suspicious evidence, re-exploration was performed at which time a small nodule was palpated in the pancreas. Frozen section of nodules along the pancreas showed fat necrosis. A radical pancreaticoduodenectomy was performed after Whipple. The pathology report stated: "Common duct showing marked dilatation to 5.5 cm with narrowing near the ampulla of Vater. Accessory pancreatic tissue found in duodenal wall. Mucosa of common duct granular but no tumor found. A segment of pancreatic duct is moderately dilated. The pancreas shows no abnormalities."

The patient had a benign postoperative course with transient steatorrhea and temporary choledochojejunostomy fistula as the only complications. A postoperative flat film demonstrated air in biliary radicles. At four years' follow-up there was no loss of weight or steatorrhea on oral pancreatin medication.

Failure to establish the benign nature of the pancreatic rest within the duodenal wall, overemphasis of the value of a single cytology report which was compatible with, but not described as diagnostic of malignancy and underemphasis of repeated guaiac negative stools may well have been the setting for a needless tragedy. It is of interest to note the absence of postoperative cholangitis despite the radiographic evidence of free communication between the biliary and enteric tracts, a clinical feature emphasized by McMillar (3).

Case 2. Ampulla of Vater with Cholangitis Simulating Calculus and Bile Duct Stricture

A 72 year old white man (572357) was troubled for three months before admission with progressive constipation without melena associated with gaseous distention and belching. During the weeks prior to admission the patient had repeated febrile episodes spiking to 104°F. The history revealed previous hypertension and passage of renal calculi. He was well nourished, febrile and slightly icteric with evidence of recent weight loss, hypertension and cardiomegaly, three fingersbreadth hepatomegaly and one fingerbreadth splenomegaly.

Guaiac stools were negative; a differential blood count was normal. The urinalysis showed a trace of bile and 1:10 urobilinogen. Blood biochemical estimations of liver function showed: cephalin flocculation negative, total protein 7.9, thymol turbidity negative, alkaline phosphatase of 44 units was ascribed on x-ray evidence to Paget's disease. A blood retention bromosulphalein of 15%, however, and failure of the gallbladder to visualize on oral cholecystogram were thought to indicate liver disease despite the normal chemical studies. Pancreatic secretion test revealed normal bile staining of duodenal aspirate, normal enzymes and low volume of bicarbonate. In the hospital the patient had two episodes of cholangitis, each associated with transient fever, icterus, guaiac positive stools and pain. A percutaneous biopsy was reported as bile duct proliferation with portal inflammation. After review of an upper gastrointestinal x-ray series, the suggestion of a Vaterian mass was noted. A clinical diagnosis of carcinoma of Vaterian ampulla was made and laparotomy undertaken. A localized mass feeling like a common duct stone was palpated at the terminus of the common duct. Duodenotomy showed it to be a Vaterian tumor, although a probe passed easily into the duodenum. Because of the precarious medical condition of the patient, a cholecystogastrostomy and posterior gastrojejunostomy were performed. Postoperatively, he did well and during the next three years he was treated with cystostomy and, later ureterolithotomy for calculus; still later a conservative reduction of an incarcerated hernia was successfully handled before he finally died seven years postoperatively. Postmortem findings revealed a hugely dilated pancreatic duct with obstructing carcinoma of ampulla of Vater.

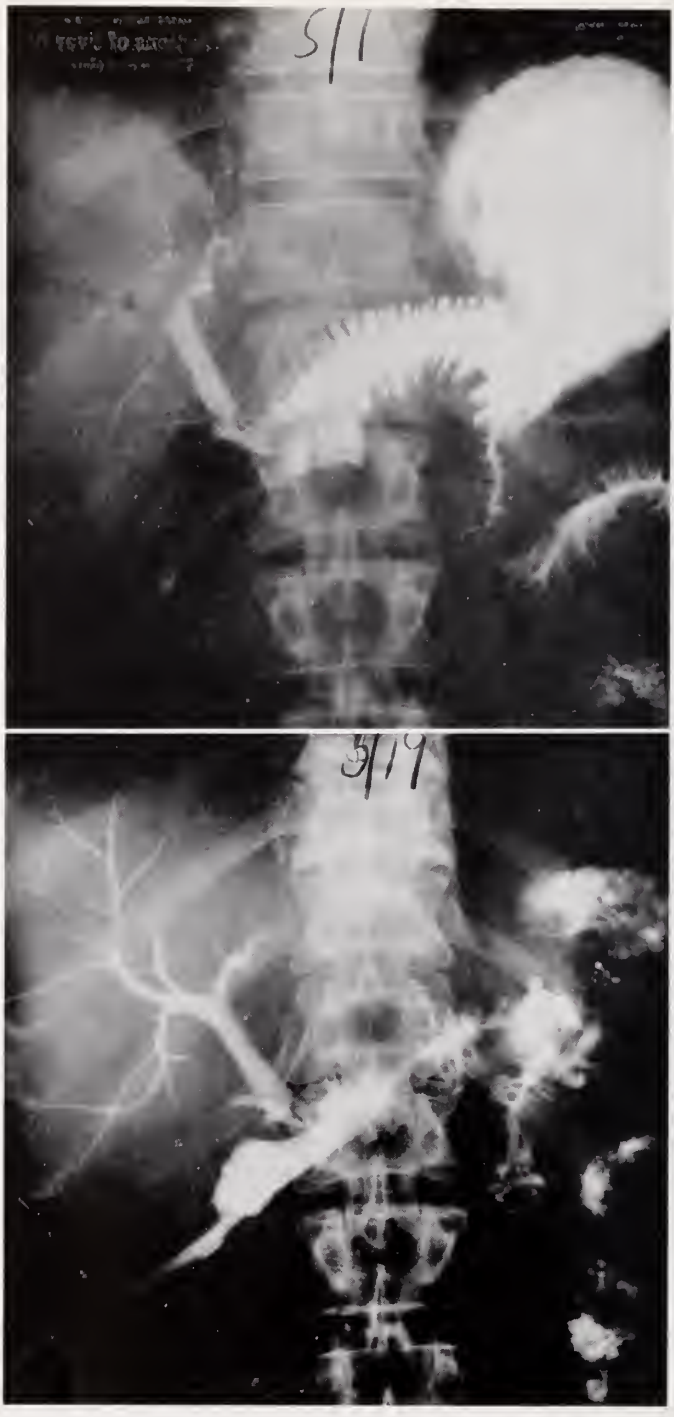
This case shows a good result from a palliative procedure which relieved the obstructive element of malignant disease. It illustrates the importance of thorough preoperative evaluation and the importance of multiple modes of diagnosis in guiding prompt surgical decisions. It also points up the phenomenon of cholangitis as a phase in the clinical history of a malignant obstruction of the distal common duct, a fact often not fully emphasized by clinicians, who clearly appreciate the other chronic features of progressive extrahepatic biliary obstruction, namely biliary cirrhosis and esophageal varices (4).

The fact that Charcot's fever may predominate clinically without enlargement of the gallbladder in malignancy is further evidenced in the following case.

Case 3. Carcinoma of the Ampulla of Vater with Fever and Episodic Icterus

A 54 year old Greek born man (190982) was transferred to The Mount Sinai Hospital with an eight month history of painless recurrent fever and weekly transient shaking chills. He had lost 13 pounds in the eight months before admission. The patient was well developed, slightly thin, icteric and had no pain. There was three fingersbreadth hepatomegaly without splenomegaly. Hemoglobin was 14 Gm%; urinalysis revealed 2+ bile and urobilinogen 1:80; alkaline phosphatase 70/SR 42; SGPT 60, SGOT 72, thymol turbidity 1.0; bilirubin 0.2 to 0.7 predominantly direct. Two stools were trace positive. Intravenous cholangiogram demonstrated a 14 mm wide common duct. Barium enema was negative; gastrointestinal series were reported normal.

A clinical diagnosis of ascending cholangitis with common duct stone was made because of the febrile course and the patient was prepared for laparotomy with antibiotics and vitamin K intramuscularly. At exploration the liver was tense but not cirrhotic. Chronic periportal lymphatic inflammation was reported on frozen section biopsy as nonmalignant. No calculi could be found at choledochotomy, and on opening the duodenum a fleshy Vaterian lesion was found; it was reported on frozen section biopsy as adenocarcinoma. A radical total pancreaticoduodenectomy and splenectomy were performed, joining the common duct and stomach to jejunum (Fig. 1A). The postoperative course was complicated by thrombocytosis, pulmonary emboli, severe antibody-induced diabetes, steatorrhea and a biliary leak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(Fig. 1B). Each problem has been handled adequately to date and the patient is home and stable eight months after his resection, on prednisone, pork insulin, decholin and pancreatic viakase.

Because of this patient's middle Eastern origin, and eosinophilia and parasitic ova in the stools, this case preoperatively suggested the differential diagnosis of intestinal infestation as a cause of Charcot's fever. Biliary obstruction by Ascaris roundworm is regularly encountered in tropical countries. Other authors have implicated F. Hepatica and C. Sinensis in China and the Far East (5). However, the importance of persistence in diagnostic work-up beyond establishing parasitic infestation is demonstrated by this case as well as the following.

Case 4. Duodenal Adenoma in a Perivaterian Diverticulum with Charcot's Fever, Amebiasis and Common Duct Gravel

A 71 year old woman (152807) was admitted to The Mount Sinai Hospital with a 21 year history of intermittent attacks of fever. In 1939 the patient first noted the onset of fever lasting 48 hours, occurring about once every ten days. There were four typical attacks in the three months prior to admission with fever to 103°F. On admission the patient had a temperature of 104°F., pulse of 80, respirations 16 and blood pressure of 150/80. She was well developed and nourished, without scleral icterus. No abdominal organs or masses were palpable. Her urinalysis demonstrated 0 bile and 1:20 urobilinogen. Differential blood count was normal and sedimentation rate between 70 and 90 mm per hour. Blood biochemical studies were as follows: bilirubin 7/3 to 5/3; prothrombin time 13/13; cholesterol 280 mg, alkaline phosphatase 60, 45 and 55, SGOT 33, cephalin flocculation negative to 2+. Of seven stools tested for blood, three were positive. Serum electrophoresis showed high gamma globulin. Duodenal drainage on two occasions was negative for ova and parasites, icterus index was 5.9, duodenal bicarbonate level was 23–59 mEq/L and amylase was also normal. Oral cholecystogram failed to visualize the gallbladder. Duodenal drainage was negative for malignant cytology (140553). Gastrointestinal series shows a large hiatus hernia without reflux and two duodenal diverticula (Fig. 2A). Urine culture and common duct bile culture showed E. coli moderately sensitive to tetracycline. Stool smear showed E. histolytica, and the patient was treated with a course of chloroquin diphosphate. A clinical diagnosis of common duct stones was made. At laparotomy a cholecystectomy and choledochotomy were performed on finding a dilated biliary tree with a chronically thickened gallbladder containing one stone and some gravel. A liver biopsy was reported as nonspecific reactive hepatitis with chronic fibrosis. A Bakes dilator #6 passed through the ampulla without difficulty. No gross pancreatic disease was noted, and no calculi were palpated in the common duct.

The patient's postoperative course was complicated by a persistent biliary fistula. The alkaline phosphatase postoperatively dropped to 8, but with the partial closure of the fistula, rose again to 20. The patient remained anicteric postoperatively with a serum bilirubin of 0.5. Six weeks following surgery the patient's temperature again spiked to 102°F. She was discharged afebrile on chloromycetin.

Her convalescence was characterized by intermittent discharge of pus and bile from the fistula with spiking intermittent fever to 104°F., and she was readmitted on November 11, 1960, thin, chronically ill, with no change in vital signs and no abnormal masses of tenderness, and a persistent, external, purulent biliary fistula. Blood count on admission showed a hemoglobin of 10.6, white blood count 9400, urinalysis revealed bile trace, normal urobilinogen.

FIG. 1A. Postoperative gastrografin study (190982) demonstrating choledochojejunostomy and gastrojejunostomy with irritable efferent jejunal loop, ten days after radical pancreaticoduodenectomy.

FIG. 1B. Fistulogram five weeks postradical pancreaticoduodenectomy. Note the normal intrahepatic radicles despite fistula.

She remained febrile for one week on chloromycetin and tetracycline. Although fistulography four months previously demonstrated communication with the common duct, at this time fistulography was nondiagnostic (Fig. 2B).

Surgical exploration revealed a dilated common duct of 25 mm diameter. The duct contained inspissated bile. The 3 mm Bakes dilator could not pass into the duodenum and a polypoid tumor was palpable against the dilator. On duodenotomy a 2 × 2 cm adenomatous broad-based polypoid lesion was found and excised. This was reported as benign adenomatous polyp. Just proximally, a duodenal diverticulum was defined into which both pancreatic and bile ducts entered separately. Sphincterotomy was performed. Liver biopsy was reported as portal inflammatory reaction with moderate bile stasis and regeneration. The patient's

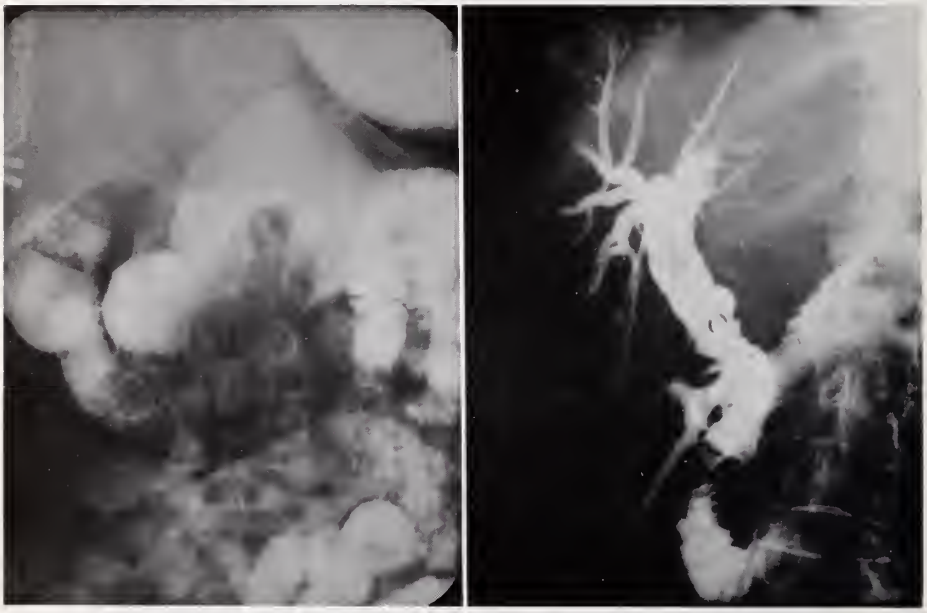

Fig. 2A. Note large duodenal diverticulum (152827) which obscures a 2 × 2 cm duodenal perivaterian adenoma just below.

Fig . 2B. Dilated hepatic radicles after first common duct exploration. Note dye does not track smoothly into duodenum, and diverticulum is not seen here.

postoperative course at this time was benign on T-tube drainage and she was discharged improved.

This patient illustrates the importance of thorough investigation at the first exploration. The persistent fever and dilatation of common duct in the absence of large duct stone was not adequately explained by the relatively benign gallbladder. More thorough evaluation of the periampullary region distorted by perivaterian diverticulae (Fig. 2) would have revealed a benign exophytic tumor which intermittently obstructed the distal common duct.

The problems associated with prolonged obstructive jaundice due to malignancy, even in the relatively young and otherwise fit patient, in whom preoperative work-up has not pinpointed a diagnostic attack, are well illustrated in the following case.

Case 5. Adenocarcinoma of the Ampulla of Vater with Progressive Jaundice, Anorexia, and Liver Disease

A 42 year old white man (188805) was admitted to the hospital with a three month history of weakness and anorexia, treated with vitamins and tranquilizers. Six weeks prior to admission, acholic stools and dark urine were first noted. The jaundice progressed on

FIG. 3. Preoperative GI study (188805) showing inferomedial indentation on duodenal sweep and superolateral impression of enlarged gall bladder.

bed rest without fever, and he was admitted to The Mount Sinai Hospital in February 1962. On admission, the patient was a slender, well-developed male, markedly icteric, with palmar erythema, skin excoriation and two fingersbreadth tender hepatomegaly. The patient had recent gross bleeding per rectum. Differential blood count was normal. Urinalysis 4+ bile, 1:320 urobilinogen. Stools were 4+ for blood, but stercobilin positive. The prothrombin time was prolonged to 27 seconds, cephalin flocculation negative, SGOT 82. Albumin 3.7, globulin 4.1 Gm%. Alkaline phosphatase 27, bilirubin 20, cholesterol 680/260. Barium enema was negative, but gastrointestinal series showed duodenal widening and medial and lateral compression (Fig. 3). The clinical diagnosis of common duct stone

was made with partial obstruction. After nephyton preparation, the patient was explored and found to have a greenish yellow tense liver and a distended gallbladder. The common duct was dilated to 4 cm. A one inch diameter nodularity or calculus was felt in the head of the pancreas. Choledochotomy failed to reveal calculi on repeated probing. Duodenotomy was resorted to with the finding of an indurated papilla of Vater. Transduodenal probing still failed to reveal stones. A sphincterotomy was performed and the duodenal wall which appeared grossly normal was sent for frozen section biopsy, reported as adenocarcinoma. When further inspection failed to reveal either hepatic or lymph node metastasis, radical total pancreaticoduodenectomy and splenectomy was performed implanting common duct and stomach into a loop of jejunum. The postoperative course was complicated at first by persistent intra-abdominal bleeding requiring a total of twelve units of blood, followed by the development of a cholemic state, with liver flap, mental obtundation, uremia, and terminal bronchopneumonia which was severe, overwhelming and finally necrotizing. SGOT was 106. Postmortem demonstrated a widespread purulent bronchopneumonia. There was no evidence of residual tumor or distant metastatic disease.

Although this malignancy falls within the criteria of surgically resectable lesions, the patient's early cholemia raises the question of staging of the massive resection. Prolonged, unrelieved obstruction with its associated liver cell damage and deficiencies may respond to preliminary decompression prior to major curative resection. This is illustrated in the following case.

Case 6. Perivaterian Pancreatic Neoplasm with Obstructive Jaundice

A 48 year old Negro woman (193405) entered the hospital for the first time with a one month history of postprandial epigastric fullness. The patient was noted to be jaundiced initially by her physician. Her stool was found to have become tan and urine dark. She had a one month history of orthopnea and dyspnea. On examination, the patient showed mild scleral icterus, a two fingersbreadth liver, a palpable gallbladder and no splenomegaly. Differential blood count revealed anemia and leukopenia with normal platelets; urinalysis revealed bile 1+, 0, urobilinogen 1:20, 1–80. All stools were tan and stool guaiacs were either negative or 1+. Blood chemistries showed albumin 3–4 Gm%, globulin 3.1–3.6, prothrombin time 18/12. Cephalin flocculation 0, alkaline phosphatase from 25 to 55 KA units and SGOT 72. Bilirubin fluctuated from 4.3/2 mg% down to 1.4/10 mg%. Gallbladder failed to visualize on oral cholecystography. An upper gastrointestinal series suggested pressure without ulceration on the second portion of the duodenum. Duodenal intubation was not tolerated by the patient. A clinical preoperative differential diagnosis was between common duct stone and obstructing malignancy. With vitamin K preparation, the patient was explored and found to have a hard 3 cm ulcerating neoplasm originating in the head of the pancreas, eroding into the duodenum. No gross evidence of hepatic or lymph node metastases was noted. Because of the tense nature of the biliary system and the liver, a preliminary cholecystostomy was performed. During the ensuing three weeks, the patient was treated with high protein diet, bile replacement, konekion and antibiotics. At the second stage, a formal radical pancreaticoduodenectomy, splenectomy, and vagotomy were performed, reanastomosing the common duct and the proximal stomach to a retrocolic loop of jejunum. The pathology report (14819) was infiltrating carcinoma of the head of the pancreas, with two metastatic lymph nodes, producing ductal obstruction. Despite thrombocytosis with postoperative pulmonary embolism, fascial wound infection and mild diabetes, the patient made a prompt recovery. She was discharged on viakase, desichol and dietary control of diabetes, returning six months later for lysis of adhesions at which time recurrent nodules were found.

This case illustrates a good result following staged resection, when the patient's exploration may be delayed so that diagnostic measures may be properly pursued. Occasionally, however, as in case 2, presentation as a toxic, acutely

ill jaundiced patient required primary attention to the toxicity, with the considerations for etiologic diagnosis secondary. A case in point follows.

Case 7. Chills, Fever, Jaundice and Stricture of the Distal Common Duct with Ulceration

This 57 year old Puerto Rican male (197228) presented with a two week history of fever, right upper quadrant pain radiating to the back, dark urine and dysuria. Fever and jaundice five years prior to admission responded without specific therapy. Physical examination on admission revealed a slender, well-developed diaphoretic icteric man in acute distress, with 103 F. temperature, rales at both lung bases, right upper abdominal tenderness and guarding and rebound. On admission, his hemoglobin was 11.2, white blood count 16000 with 88 pmn's, 12 lymphocytes, and sedimention rate 60. Urinalysis: bile trace, urobilinogen 1:640; the stool was brown and guaiac positive. Blood chemistries were as follows: albumin 2.8, globulin 4.3, bilirubin 3 1.2, cholesterol was 125, SGOT 34, alkaline phosphatase 20, cephalin flocculation plus, thymol turbidity 1.2. X-ray showed nonspecific small bowel patchy dilatation. On hydration, intravenous, antibiotics and aspirin, the patient ran a toxic course, with increasing right upper quadrant tenderness suggestive of suppurative cholecystitis or cholangitis. Blood cultures grew pneumococcus.

Clinical diagnosis of ascending cholangitis with common duct stone was made. Exploration was performed for urgent decompression. At operation, the pertinent findings were hepatomegaly, focal edema of the hepatic duodenal ligament and common duct dilation. The gallbladder appeared normal. On thorough pancreatic palpation, a nodularity was felt near the termination of common duct. Choledochotomy failed to demonstrate calculi, and clear golden bile drained from the common duct. On duodenotomy clear whitish drainage from a pancreatic ostium in duodenum was noted, but an ampulla of Vater could not be identified, the common duct probe finally entering the duodenum, through what appeared to be mucosa. Liver biopsy was read as consistent with extrahepatic obstruction. Cholecystectomy revealed a normal gallbladder mucosa and no calculi.

The postoperative course of this patient was marked by four subsequent febrile episodes. The temperature subsided with chloromycetin and tetracycline. E. coli was cultured from the bile. Stool guaiacs have remained negative. Postoperative T-tube cholangiogram (Fig. 4) demonstrated mucosal ulceration at the junction of common duct and duodenum for 1.5 cm. However, despite gastrointestinal series evidence of patent choledochoduodenal junction, the patient demonstrated partial biliary obstruction for several weeks. Duodenal secretion test results: volume 6.1 ml, HCO_3 120, amylase enzymes 63 and bile 2+ in the duodenal drainage. Late blood cultures grew Str. viridans.

Glenn *et al.* have summarized the bacteriologic findings in cholangitis, and find the most common offenders to be E. coli, B. pyocyaneus, Streptococcus, enterococcus and P. vulgaris (6). The organisms are of normally low grade, invasive pathogenicity producing only superficial mucosal pathology, rarely invading the portal vein with endophlebitis and fatal septicemia. Chloromycetin, tetracycline and streptomycin are all concentrated in bile, and therefore may be more effective than other resistant biliary tract infections.

Although malignancy has not been ruled out in this case, as it might better have been by duodenal biopsy at the time of duodenotomy, it may fall into the group of primary cholangitides without obstructive lesions. This syndrome of recurrent pyogenic cholangitis has best been described by Cook and MacFadyen:

1. The cases present with Charcot's fever.
2. There is a history of previous attacks.

3. E. coli is the usual offending organism.

4. The infection leads to the formation of stones in the common duct and biliary passages. Death may occur before the formation of stones. Surgery to promote drainage and where indicated to remove stones, combined with antibiotics, appears to be life saving, although the infection may persist.

FIG. 4. Postoperative cholangiogram (197228) demonstrating suspicious mucosal ulceration of distal 2 cm of common duct.

McMillar also has described a case of nonobstructive cholangitis apparently originating in the gallbladder, with findings limited to common duct edema with no obstruction to probing into duodenum (3). This condition may be associated with the chemical peritonitis of acute cholecystitis and account for the transient jaundice, without sequelae that was occasionally seen here in a case of acute obstructive cholecystitis.

A condition described as primary sclerosing cholangitis, with thickening

and narrowing of bile ducts, may present as jaundice, pain in epigastrium or right upper quadrant and fever (7). This condition, however, responds to steroids and prolonged tube drainage.

DISCUSSION

In reviewing these cases, several ancillary points deserve re-emphasis.

1. Cholangitis, although found most frequently with stone or benign stricture, is also a phenomenon of malignant ulceration or stricture. The presence of bacteria ubiquitous in the portal tracts is not sufficient to produce infection. When the common duct and sphincter are infiltrated by neoplasm, the disruption of normal choledochal peristalsis may be as important in the initiation of cholangitis as the element of simple obstruction.

2. Preoperative investigations, where possible, should include a study of urinary bile pigments, duodenal secretion, response to secretin, and cytology studies. Stools should be examined for blood and parasites. X-ray studies should include intravenous cholangiography and spot films of duodenal sweep on gastrointestinal series. Dreiling and his co-workers have reported 94 per cent accuracy with this combination in the diagnosis of carcinoma of the pancreaticoduodenal region (8).

The presence of bile in normal concentration on duodenal drainage for the secretin test is characteristic of the cases recently studied with thorazine-induced jaundice. This entity in most other respects is clinically indistinguishable from other causes of obstructive jaundice (9). Other diagnostic aids preoperatively in the chronically, but not acutely ill patient, include percutaneous peritoneoscopy, which can both identify the dilated gallbladder of malignant obstruction and guide the needle for a percutaneous liver biopsy, and hepatodochogram which may implicate obstruction, and obviate unnecessary surgery.

3. A clear surgical view of the distal end of the common duct is essential to the diagnosis of early neoplasms, as emphasized by Cole (10) and biopsy of this region, when other methods have failed, may be vital in determining the further course of therapy.

4. Even when resection of the early malignancy is technically not possible, adequate double by-pass as illustrated by our second case, may provide excellent palliation. In addition, staged procedures in the severely obstructed or toxic patient may permit successful resection without operative mortality.

5. When preoperative diagnostic measures have failed to demonstrate a local cause for severe ascending cholangitis, one should bear in mind the possibility of parasitic or even primary catarrhal etiology of the disease, and be satisfied with a first stage by-passing procedure. Surgical diagnosis via laparotomy and duodenotomy should not be deferred at this point.

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Eosinophilic Granuloma of the Stomach

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Eosinophilic infiltration of the gastrointestinal tract was not mentioned in the literature until 1937 when Kaijser published three cases, of which two were believed to be due to neoarsphenamine-sensitivity and one secondary to onion ingestion (1). Subsequently, the entity of eosinophilic infiltration and granuloma of the upper gastrointestinal tract, particularly of the stomach became more frequently recognized. However, the majority of the published reports referred to patients who were either symptomatic as a result of their eosinophilic lesions or who had an eosinophilic infiltration in response to allergic hypersensitivity, displaying blood eosinophilia as a prominent feature. In 1952, Barnett and Kazmann could find eight cases only, documented with a normal eosinophilic count in the entire literature of symptomatic eosinophilic granuloma of the stomach (2). Of these, six had been reported by Vanek in 1949, the latter representing the first reference to an eosinophilic granuloma of the stomach without a presumed hypersensitivity etiology (3). In addition, Vanek was able to show that the granulomata did not necessarily project into the lumen of the stomach. In 1956, Rigler reported nine cases of gastric granuloma with eosinophilic infiltration; in four only were the gastrointestinal symptoms possibly attributable to the lesion (4). All of the lesions were polypoid masses.

A case is reported here of eosinophilic infiltration in a granuloma of the stomach noted incidentally on pathological examination following gastric resection for massive upper gastrointestinal bleeding.

CASE REPORT

N.M. (197253), a fifty year old Negro female was first admitted to The Mount Sinai Hospital on June 28, 1962, because of hematemesis. The patient, a very mild alcohol consumer for ten years, began to drink excessively during the six months preceding admission to the hospital. She had been in reasonably good health until one week prior to admission when she noted some shortness of breath on exertion and epigastric pain unrelated to meals. She had suffered heartburn for many years, as well as occasional fatty food intolerance and epigastric distress. One day prior to admission, the patient had six to eight episodes of bloody vomitus and, on the day of admission, she passed several tarry stools, became dizzy, and markedly dyspneic. Her past history was otherwise noncontributory except for a previous hysterectomy for a fibroid uterus.

On admission, the patient was perspiring with a pulse rate of 120 and a blood pressure of 80/0. The liver was four fingersbreadth below the right costal margin. The spleen was not felt. The hematocrit was 22%, the white count was 9000, with 80 segmented polymorphonuclear leukocytes, 6 band forms, 11 lym-

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phocytes, 1 eosinophil, 1 basophil, and 1 monocyte. The electrocardiogram was normal. An emergency barium swallow at the time of admission revealed no abnormality of the upper gastrointestinal tract. Esophagoscopy revealed no significant findings. Gastroscopy revealed no lesions of the gastric mucosa. During the 36 hours following admission, the patient had several more episodes of tarry stools and bloody vomitus. She required 5500 ml of blood in order to maintain a hematocrit of 40%. Because of the history and the suggestion of a mucosal lesion, operation was undertaken as an emergency procedure. During the operation there were several small superficial oozing areas on the fundus evident after handling mucosa in this area. These were not considered to be the source of the hemorrhage and were not typical of gastritis. As there was no clear evidence of the source of bleeding, a vagotomy and fifty per cent gastrectomy was done. On gross examination of the specimen, there was a 2 cm irregular submucosal plaque on the greater curvature aspect of the stomach near the antrum and well away from the oozing in the fundus. On microscopic examination, this plaque was a granulomatous lesion with fibroblastic activity and marked eosinophilic cellular infiltration; the pathologist's report was an eosinophilic granuloma of the stomach. The mucosa overlying this submucosal lesion was intact.

The patient's postoperative course was uneventful. On follow-up visits, she had had no recurrence of gastrointestinal symptoms or bleeding.

DISCUSSION

In 1961 Ureles outlined a classification of idiopathic eosinophilic infiltration of the gastrointestinal tract (5). He recognized two categories: one a diffuse eosinophilic gastroenteritis, and the second, circumscribed eosinophilic infiltration, either regional or polypoid. In the first group, further subdivided into three smaller groups, eosinophilia was a prominent feature, and Ureles advised that these cases would be served best by steroid therapy. However, in the second group, where eosinophilia was not a feature, surgery was recommended as the treatment of choice and it was curative. Our patient would fall into the second category, *i.e.*, small localized eosinophilic granulomata of the stomach. This lesion is distinguished from other eosinophilic granulomatous lesions, especially of bone, where the predominant cell is the histiocyte, by the pre-eminence of the fibroblast.

Since this patient exhibited no eosinophilia and no history of allergic manifestations in any organ system, it is of interest to speculate on the etiology of the gastric eosinophilic granuloma. In 1954, Sherman and Moran produced polypoid granulomata of the stomachs of fifteen rabbits by means of exogenous foreign bodies (6, 7). By using gastric juice in 25 other rabbits more severe changes were produced. In addition, they presented six cases of gastric granulomata, five with ulcer, and raised the question of whether degenerated smooth muscle or fibrous tissue played a part in the formation of these granulomata. The only predisposing feature present in this patient's history was that of

marked increase in alcoholic intake during the six months immediately preceding the acute episode of bleeding.

It is interesting that there have been several reported cases of eosinophilic infiltration where the diagnosis had been made preoperatively, generally in patients with an eosinophilia similar to the observations in Glenn's case (8).

It should also be noted that the lesion seen grossly at operation appears to be similar to that seen in granulomatous enteritis. Maloney (9), as well as Lynch (10) has called attention to this in association with pyloric obstruction, a frequent concomitant pathological entity. In these cases, the lesion was more extensive, involved the muscularis mainly, spared the mucosa and serosa, and appeared only slightly in the submucosa.

SUMMARY

A case of massive upper gastrointestinal bleeding requiring emergency gastrectomy is reported. Except for the presence of an eosinophilic granuloma near the antrum of the stomach no definite cause for the bleeding could be found. The possible relation of this lesion to the patient's bleeding and a review of the literature are presented.

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A Practical Approach to the Treatment of Chronic Intractable "Functional" Pain

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The patient with chronic refractory pain is not an uncommon problem for the medical practitioner. Whether the pain be localized to the abdomen, back, leg or any other body part or area, the histories of these patients are often remarkably similar. At the initiation of the symptom, either isolated or accompanied by other complaints, the appropriate medical work-up is executed with the result that either no pathology is uncovered to explain the origin of the pain, or that some pathology is found which is thought to be contributory to the pain and is appropriately treated. In the first instance the pain may be labeled "functional" or "psychological" immediately, or this evaluation may be delayed until repeated work-ups, drug therapies, or more stringent therapies are exhausted and the patient continues to complain of pain. In the second instance, the organic pathology suspected as the basis of the pain is treated or corrected with either transient or no improvement. The treatment may be as complete as alcohol injection of nerve roots, transection of nerves, or cordotomy. Often the patient develops drug addiction. The tremendous demands upon the treating physician(s), the enmeshment of families and financial depletion, and the great frustration to all involved are no less horrendous than the problems presented by a chronic wasting disease.

As a result of our experience on the Psychiatric Service in the treatment of patients with chronic refractory "functional" pain, we have developed a practical therapeutic approach to the problem. Our patients were usually referred by the other medical and surgical services of the hospital.

Before outlining the treatment plan, a definition of "functional" or "psychological" pain is necessary. We will define such pain as that which has no demonstrable organic etiology after complete medical work-up is performed, or which cannot be explained by the pathology known to be present or revealed by medical work-up.

THE TREATMENT PROGRAM

1. It must be ascertained that the patient's pain falls within the functional category. This has usually been established by the referring physician. If not, the necessary work-up is completed through consultation. It is extremely important that organic etiology be ruled out. If this is not done, the future course of the patient's hospitalization will be besieged by doubt on the part of the treating physician(s), sporadic tests and laboratory procedures will be performed, and pandemonium will reign.

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2. The referring physician is apprised of the treatment plan and advised of the future harassment he is likely to receive from his patient. Pain often fills a psychological "need" and is not given up easily by the patient. Requests for discharge, furtive phone calls to "get me out of here and give me some real medicine" are not uncommon.

3. The patient must be treated in the hospital. Previous experience has shown that the patient will not otherwise take the prescribed medication, revert to the use of narcotics, fail to keep appointments with the psychiatrist, and in general be unwilling to actively participate in the therapeutic program. Continuous supervision is necessary.

4. The family is advised of the general outline of our treatment plan, and is seen by a social worker in regular visits or as the need arises. Pain is not an isolated phenomenon. In our patients especially, it is a complex psychophysiological situation often involving the patient's relationship with his family. The manipulation of family by a patient through illness is often observed by the medical practitioner; it is unusual not to find it in the particular group of patients with whom this paper is concerned.

5. When the patient's pain has been ascertained as "functional," medication given to the patient should be an appropriate psychiatric drug, *e.g.*, tranquilizers and anti-depressants. Our patients have revealed uniformly underlying psychological illness; therefore, medication is directed at this illness. In patients with known organic pathology, an appropriate or usual narcotic may be given in the usual dosage together with the selected psychiatric drug. *All narcotic medication should be discontinued or the patient withdrawn if addicted,* when the patient's pain is considered entirely functional.

6. The treatment plan is outlined to the ward staff, nurses and doctors, and all are advised of the difficult treatment course ahead. Patients will prod, pressure, manipulate, carry on, and may do just about anything to sabotage the treatment program. Consistency and firmness are absolute necessities on the part of the professional staff. These problems diminish as the patient is involved in the next step.

7. Intensive psychotherapy. Here the understanding of the patient's problem is embarked upon and the psychological roots of his pain explored. This step, together with the use of tranquilizers (*e.g.*, Thorazine®, Sparine®, Stellazine®) and/or anti-depressants (*e.g.*, Tofranil®, Elavil®) form the cornerstone of our treatment plan. However, the entire program may be wrecked if all steps are not meticulously followed.

The following case histories will illustrate our treatment plan.

CASE REPORTS

Case 1. G.S. is a 61 year old, white, married, left-handed male, referred by the Neurology Service of our hospital, with a nine-month history of "terrible pain in the right hand." The patient was found first by the psychiatric consultant in the neurology ward bathroom banging his head on the sink and yelling of his terrible pain. His right hand revealed a flexion paralysis of the third, fourth and fifth fingers, and an extension paralysis of the first and second fingers. There was a moderate degree of swelling about the

interphalangeal and metacarpal-phalangeal joints. After a few minutes of discussion the patient's complaints temporarily ceased and he agreed to his transfer to the Psychiatric Service of the hospital. A review of the patient's records showed that he had received Darvon®, codeine, Atropine®, Demerol®, Phenergan®, and Phenobarbital® in apparent random alternation or combination, resulting in either transitory or no relief. The patient's response to anti-pain medication was not related to the pharmacological action of the drug(s) received. Upon admission to the Psychiatric Service all previous medication was discontinued. The patient was placed on Sparine® (promazine) 100–200 mg every two hours prn for complaints of pain, receiving up to a total of 1000 mg/daily. It was discovered in psychotherapy that an underlying depression existed, and Elavil® (amitriptyline) 75 mg/daily was initiated and gradually increased to 150 mg/daily. It was learned that the patient's symptoms began shortly after he retired from a highly active outdoor job involving much physical effort and high responsibility. Retirement also brought about continuous contact with his wife, considerable change from the long hours of his working career, and a mounting hostility felt but never expressed by the patient (though often by the wife). As the relevant psychological problems were explored and discussed in psychotherapy, and tranquilizing and anti-depressant medication was maintained, complaints of pain diminished in intensity and frequency. The paralyses and edema of patient's right hand gradually resolved. No organic etiology had been found, and we considered the paralyses hysterical in nature with the edema secondary to the frozen position of the hand and consequent stasis. X-rays of the hand revealed an absence of joint changes. Following three months of in-patient treatment he was discharged to the Out-patient Psychiatric Service on a maintenance dose of the medication received while in the hospital (Elavil® and Sparine®). The patient's wife died of metastatic cancer three months following his discharge from the hospital, resulting in a flare-up of complaints of pain, and a need for increased medication. These complaints gradually diminished and within three months following his wife's death the patient was totally symptom free. All medication was discontinued and the patient seen for occasional follow-up visits in the Out-patient Department. A seven-month follow-up reveals no return of symptoms and the patient is free of depression.

Case 2. E.S. is a 55 year old, white, unemployed, married housewife, referred by the Neurosurgical Service with the complaint of "chronic refractory back and leg pain of seven years' duration." During the course of her illness the patient had received the gamut of anti-pain medication, had been addicted to Dilaudid®, and caused a large portion of her husband's income to be channeled into her medical treatment. Six years after initiation of the symptom of pain, epidural alcohol blocks were performed with no relief. One year later a cordotomy was performed with no postoperative relief of pain, which was followed in four days by an acute paranoid schizophrenic break (the first overt psychiatric illness suffered by the patient). Recovery from this acute psychotic episode was effected in one month and the patient returned to her rounds of physicians' offices and medications. Five months later the patient was admitted to the Neurosurgical Service of our hospital for a re-evaluation of her complaint. A thorough work-up revealed no organic pathology, and psychiatric consultation was requested. At the time of her transfer to the Psychiatric Service the patient had been receiving Demerol®, Dilaudid®, Meprobamate®, vitamin B_{12}, Librium®, and Phenergan®. Again, these drugs had been administered in random alternation or combination with transitory or no relief and a generally inconsistent response. (The reason for the use of these drugs in this fashion is quite understandable. The treating physician is faced with the problem of alleviating his patient's pain, and if one drug is unsuccessful he will try another. The patient's inconsistent pattern of response leads to the above described pattern of administration of anti-pain medication.) The treatment procedure as outlined above was initiated. All previous medication was discontinued (the patient was not addicted to Dilaudid® at the time of this hospitalization) and the patient placed on Sparine®, 100–200 mg every two hours when necessary for pain, at first receiving as much as 1000 mg/daily in the earlier days of her treatment. An underlying severe depression was rapidly revealed and anti-depressant medication was added (Tofranil®, 50

mg t.i.d., later changed to Elavil® 50 mg t.i.d.). The patient was discharged following six weeks of in-patient treatment and was followed for seven months in psychotherapy (maintained on Elavil®) up to the writing of this paper. Her complaints of pain became infrequent, there was no further use of narcotic medication, rounds of physicians' offices did not recur, and she entered into a relatively non-chaotic period of marriage.

Case 3. J.L., a 22 year old, white, unmarried female secretary, noted the development of pain and swelling in her right foot in the spring of 1959. In November 1959, a diagnosis of "lime deposits on the nerve" was made and this was "scraped" under local anesthesia. Healing was protracted and the wound drained for several months. In December 1959, the patient began to complain of thigh pain which gradually spread to her back. From this time until November 1960 she was seen by numerous physicians, and received various treatment ranging from corsets to traction. In November 1960, myelograms revealed two herniated discs and surgery was performed. The postoperative course was characterized by severe pain and in February 1961, laminectomy and spinal fusion were performed. The patient left the hospital in March 1961, but with considerable back pain. She developed a "pelvic tilt" and walked with a limp. In July 1961, symptoms of pain became so severe that hospitalization was required. During the period of five months between discharge post-laminectomy and rehospitalization in July the patient was on continuous anti-pain medication, often opiates. No evidence of organic disease could be found in this five-month period, and the pain expressed by the patient could not be explained by the known pathology. Further work-up on the Neurosurgical Service in July was unrevealing and psychiatric consultation was requested. The patient's three-month course on the Psychiatric Service was chaotic and stormy. She wept, harangued, pleaded for anti-pain medication and dramatically dragged herself about the corridors. She often called the referring physician, accused him of abandonment, and provoked her family into an abortive attempt to sign her out of the hospital. During this period the patient was weaned from her narcotic medication and chlorpromazine (Thorazine®) substituted. She was involved in psychotherapy and relevant psychological problems were explored. At discharge, following ten weeks of treatment on the Psychiatric Service, the patient continued to complain of occasional pain, but with great decrease in intensity and frequency. She has not since resorted to narcotic medication, nor has there been any further need for corrective or surgical procedures. At follow-up, twenty-one months after discharge, the psychiatrist treating her privately reports her to be virtually free of pain.

Case 4. A 61 year old married, white, male executive, jointly treated by an internist and a psychiatrist for the complaint of chronic excrutiating abdominal pain of many years' duration, was admitted due to increasing use of narcotic medication, increasingly severe pain, and decreasing ability to function as a high level executive in a large corporation. Abdominal pain had initiated approximately forty years prior to this admission. At age 25 an appendectomy and cholecystectomy were performed, ostensibly for abdominal pain. At age 31, a gastroenterostomy was performed, again for abdominal pain, but without specific disease having been discovered. At age 41 a gastrectomy was performed and there is no record of ulcer or other pathology having been discovered. All of these procedures offered no relief of pain. About one year postgastrectomy the patient entered the Armed Forces with the rank of Lieutenant Colonel, and during his period of service and the following nine years remained pain free. In 1954, abdominal pain commenced with great severity with no response to the gamut of anti-pain medication. In 1957 an exhaustive and complete work-up was performed and no etiology for the abdominal pain discovered. The period between 1957 and the patient's hospitalization on the Psychiatric Service in 1961 revealed progressive pain and disability. Upon admission the patient's previous medications were entirely discontinued and promazine was substituted, up to two grams daily. Intensive psychotherapy immediately commenced and the staff steeled itself to this particularly demanding and vociferous patient. At the time of discharge, two months following admission, the promazine had been reduced to out-patient maintenance levels (200 mg/day) and the patient no longer complained of pain. One year following discharge from the Psychiatric Service, the patient's

physician informs me that there have been no further complaints of pain, but that the patient continues to use intermittent small doses of codeine. The latter is not an addiction but appears to gratify some psychophysiological need as well as to serve as a weapon in the manipulation of the patient's family.

SUMMARY

These patients are representative of the group categorized as having "chronic intractable functional pain." The purpose of this paper has been to illustrate the importance of recognizing this particular problem, and to outline a specific, relatively nonhazardous, and often successful treatment program. The necessity for hospitalization of this type of patient should be emphasized.

ABSTRACTS

Papers Presented Before the Research Club of The Mount Sinai Hospital

New York, N. Y.

Effect of Growth Hormone on the Metabolism of Pyruvate and Lactate. Peh Ping Ho, M.D. and Rudolph Weil, M.D. From the Nutrition Laboratory.

Blood levels of pyruvic and lactic acids in the dog were found elevated under the influence of Growth Hormone (GH) and a glucose load. The concentration of pyruvate was relatively much more increased than that of lactate.

The same results were obtained in experiments with infusion of free fatty acids with or without that of glucose.

It is concluded that the enhanced values of pyruvate in GH-treated dogs result from an inhibition of the oxidative decarboxylation of this compound due to the accumulation of acetyl CoA from fatty acids in the tissue. The increase in lactic acid is considered the result of the reductive conversion of pyruvate into lactate, a reaction which is coupled with oxidative glycolysis and depends, therefore, on the adequate availability of intracellular glucose.

Studies on Small Intestinal Motility. Gerald Friedman, M.D., Jerome D. Waye, M.D., Leonard A. Weingarten, M.D., and Henry D. Janowitz, M.D. From the Department of Gastroenterology.

A method for the simultaneous measurement of intraluminal pressure changes at three separate sites in the proximal small bowel has been devised. The method consists of employing a system of three polyvinyl tubes through which pressures are measured via 3 mm oval windows placed in tandem 5 cm apart. The three ends of the tubes were connected to Sanborn pressure transducers, and the system was perfused with water. The pressures exerted through the windows of the tubes were recorded by a Poly-viso recorder equipped with strain gauge amplifiers. The positions of the apertures were monitored initially by fluoroscopy and later confirmed by x-rays.

The method provides a means of 1) characterizing contiguous segments of proximal small bowel by wave analysis, 2) estimating sequential activity, 3) determining response to pharmacologic agents, and 4) comparing total activity and type of activity present in various pathologic entities of the small intestine.

The Pathologic and Physiologic Changes Associated with Pelvic Canine Liver Homotransplantation in the Untransfused, Unprepared Recipient. Arthur Sicular, M.D., Lewis Burrows, M.D., Stanley Edelman, M.D., Hishashi Nikaidoh, M.D., Fiorenzo Paronetto, M.D., David A. Dreiling, M.D., and Allan Kark, M.D.

Methods were developed for a surgically feasible technique for the pelvic canine transplantation of the entire liver, without the use of blood transfusion, shunts or plastic grafts. Hypothermic dextran perfusion was utilized for anoxic tissue preservation. Modified anatomic revascularization was successfully

worked out without interfering with recipient liver blood supply. Thirteen recipient-donor pairs have been performed to date, with two survivors exceeding previous published reported survivals, and three other long term survivors, with only two technical failures, among the last nine.

The evolution of liver homograft rejection has been observed with the technique of serial Menghini needle biopsy. Ancillary serum biochemical changes have been followed, along with clinical observations on the recipient dog. These results suggest that functioning liver is immediately achieved, and subsequently a rejection process analogous to that already described in kidney and other organs proceeds in the unmodified recipient, with mononuclear infiltration replacing hepatic parenchymal cells which are destroyed beginning after the fourth day of successful transplantation. Bile flow patterns reflect the changes observed in parenchymal tissue. Respiratory infection is a major complicating factor of these procedures.

Cardiodynamic and Electrocardiographic Effects of Ryanodine in Normal and Digitalis Toxic Dogs. Melvin Kahn, M.D., Irving Shiffman, M.D., Leslie A. Kuhn, M.D., and Thomas E. Jacobson, M.D.

The electrocardiographic and cardiodynamic effects of ryanodine were investigated in normal dogs and in dogs with experimentally induced digitalis arrhythmias. Ryanodine, 10 to 15 μg/Kg, was administered intravenously to 11 normal anesthetized dogs. Without a change in cardiac rhythm, mean cardiac output fell from 3.9 to 3.0 L/min. ($p < .01$) and elevation of left ventricular end-diastolic pressure was noted. There was no significant change in mean aortic pressure. Ryanodine produced in sequence, peaking of the T waves, broadening and flattening of the P waves with loss of the PR segment and sinus slowing. Doses of 25 to 50 μg/Kg produced supraventricular tachycardia with rapid ventricular response. This was followed by atropine resistant supraventricular bradycardia with or without paroxysmal atrial arrest. The QRS complex was unaltered.

Ten dogs were primed with intramuscular digoxin for five days and then given 0.5 μg intravenously at 30 minute intervals on the experimental day. When a ventricular tachycardia or A-V dissociation was produced and maintained, ryanodine 8 to 18 μg/Kg was infused. Within ten minutes the idioventricular rhythm was abolished in all animals; in 8 by abrupt arrest of the ventricular focus and in 2 by progressive slowing with sinus capture. The QRS complex and PR interval were unaffected. Electrocardiographic changes attributable to ryanodine alone then appeared.

It is concluded that ryanodine reverses digitalis induced ventricular arrhythmias by suppressing ventricular pacemakers but in addition has a negative inotropic and complex chronotropic action.

Cardiorenal Studies in Complete Heart Block. William G. Stein, M.D., Ephraim Donoso, M.D., Melvin Kahn, M.D., and Charles K. Friedberg, M.D.

This study was undertaken to evaluate the etiologic role of bradycardia and other factors contributory to congestive heart failure observed in some patients with complete heart block. Patients with persistent slow idioventricular rhythms

with or without overt congestive heart failure were given progressively increasing daily sodium loads by mouth until signs of heart failure or gastrointestinal intolerance occurred. Daily urinary sodium, chloride and potassium, endogenous creatinine clearance and body weight were determined. Venous pressures were obtained when indicated. The studies were performed during the period of complete heart block with slow idioventricular rates and were repeated two to three weeks following implantation of an internal cardiac pacemaker.

One patient, with an idioventricular rate of 30 to 38 per minute and a glomerular filtration rate (GFR) of 41 ml/min. excreted up to 30 mEq of sodium per day with the development of progressive heart failure as manifested by positive sodium balance, weight gain and system venous hypertension. With a paced heart rate of 66/min. sodium excretion increased to 270 mEq/day before manifestations of heart failure appeared. A second patient, with an idioventricular rate of 28 to 44/min. and a GFR of 65 ml/min. excreted up to 290 mEq of sodium daily before heart failure was manifest. When electrically paced at a heart rate of 66/min., sodium excretion rose to 420 mEq/day without an increase in weight or venous pressure. A third patient with an idioventricular rate of 30 to 38/min. and a GFR of 76 ml/min. excreted up to 430 mEq of sodium per day without developing heart failure.

It is concluded that the bradycardia of complete heart block contributes to fluid retention and heart failure. Other factors, such as myocardial damage and primary renal disease are also significant. It is further concluded that electrical pacemakers have a definite clinical application in the treatment of patients with congestive heart failure secondary to complete heart block, the response being modified by intrinsic myocardial and renal factors.

Maximal Bicarbonate Fluid and Amylase Output of the Dog Pancreas. Jack Hansky, M.D., Osvaldo Tiscornia, M.D., Claude V. Perrier, M.D., Henry D. Janowitz, M.D., and David A. Dreiling, M.D.

This paper presents the results of stimulation of the cannulated dog pancreas with increasing doses of secretin and pancreozymin. Three types of experiment have been performed using:

1. Single rapid intravenous injections of secretin
2. Constant intravenous infusions of secretin
3. Constant intravenous infusions of pancreozymin

With single rapid intravenous injections of secretin (1–15 units/Kg) and continuous intravenous infusions (1–16 units/min.), increased doses produced increased volumes of pancreatic juice and bicarbonate outputs up to a maximum. This maximum bicarbonate output of the pancreas was reached at doses ranging from 7.5 to 12.5 units/Kg for single injections, and 4–16 units/min. for infusions. In each dog supramaximal doses led to a fall in juice volume and bicarbonate output, unaccompanied by side effects.

With constant infusions of pancreozymin in doses of 0.125–2.0 units/Kg/min., increased doses produced increased volumes and amylase outputs up to a maximum. The maximum amylase output occurred with doses of 0.5 units/Kg/min.

in 3 dogs, 1.0 unit/Kg/min. in 4 dogs and 2.0 units/Kg/min. in 2 dogs, supramaximal doses in each case giving no change or a fall in amylase output.

The coefficients of variation were smallest in repeated experiments employing the maximal doses of both pancreozymin and secretin; on this basis we propose the use of maximal levels of stimulation in studies of inhibition of pancreatic secretion. Also, the measurement of maximum secretory capacity in man may allow quantitative assessment of secretory impairment.

The Effect of Fasting on Glyceride Synthesis by Hamster Small Intestine. Arthur M. Gelb, M.D., Morton I. Davidson, M.D., and Jacques I. Kessler, M.D.

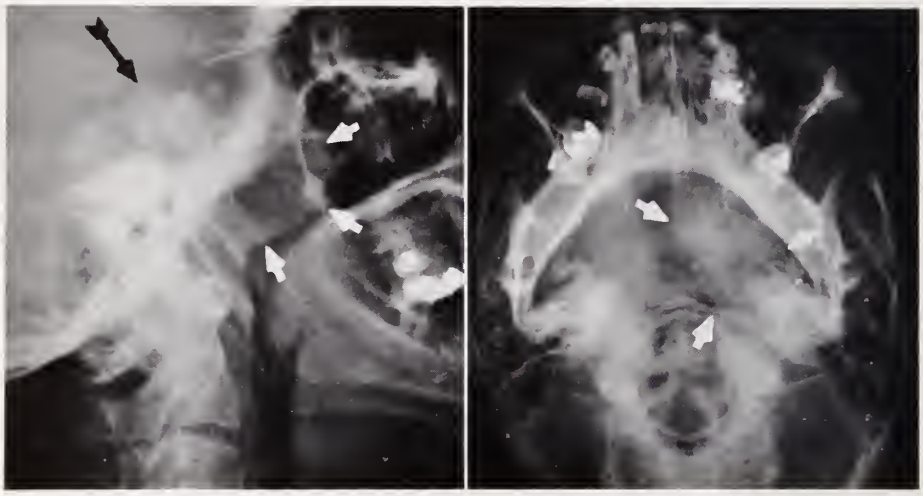
As part of a study on the effect of nutrition on glyceride synthesis by the small bowel *in vitro*, the effect of fasting on this process was investigated. Inverted slices of hamster small intestine, sacrificed after varying periods of fasting, were incubated in a medium to which C^{14} labeled myristic acid (14 carbon) had been added. Previous work indicated that in comparison with other fatty acids, myristic acid is esterified to the greatest extent *in vitro*. After incubation, lipids were extracted with Dole's solution. Nonesterified lipids were removed with alkaline ethanol. Per cent esterification of myristic acid per 100 mg of intestine in fasted animals was compared to that occurring in simultaneously incubated control animals. Fasting for periods of 4, 8 and 12 hours produced no changes. After 16 to 18 hours of fasting there was an 11.6 per cent decrease in esterification as compared to controls. After 22 to 24 hours of fasting there was a 16.2 per cent decrease. In preliminary experiments, the decrease in esterification produced by fasting was only partially reversed by the administration of parenteral glucose prior to sacrifice.

RADIOLOGICAL NOTES

CLAUDE BLOCH, M.D., AND HARVEY M. PECK, M.D.
New York, N. Y.

CASE NO. 219

A 45 year old male was admitted to the hospital following a grand mal convulsion. History revealed that "memory lapses" had occurred during the past year and these had become more frequent recently. There had been occasional generalized headache without nausea or vomiting. Visual acuity had worsened



Case 219, Fig. 1A. Lateral radiograph of the skull shows extensive destruction of the sella turcica and sphenoid sinus. A 2.5 cm mass of dense mottled calcification overlies the level of the dorsum sellae (black arrow). A large soft tissue mass extends into the nasopharynx from the base of the brain (along arrows).

Case 219, Fig. 1B. Basal radiograph of the skull reveals the calcification eccentrically located to the left of the midline (between arrows). The destructive process involves the anterior margin of the foramen magnum, both petrous tips and the basal foramina. Both greater sphenoid wings are also involved, more marked on the left.

in the past few years requiring a change in corrective lenses. Neurologic examination showed pallor of the optic discs bilaterally more marked in the temporal areas. Examination of the visual fields demonstrated a right homonymous defect. EEG showed abnormal activity over the entire left hemisphere particularly in the left temporal zone. There were no other positive findings. An intracranial neoplasm was suspected with left fronto-temporal localization.

From the Department of Radiology, The Mount Sinai Hospital, New York, N. Y.

Radiographic examination of the skull (Figs. 1A, 1B) showed an extensive destructive process which involved the sella turcica, sphenoid sinus, anterior margin of the foramen magnum, both petrous tips, and both greater sphenoid wings, more marked on the left. A 2.5 cm mass of dense mottled calcification was located in the middle cranial fossa to the left of the midline at the level of the dorsum sellae. A large soft tissue mass extended forward from the base of the brain into the nasopharynx. Left carotid angiography showed marked elevation and straightening of the carotid siphon and moderate displacement of the anterior cerebral artery to the opposite side. Some vascularity was noted along the anterior portion of the nasopharyngeal soft tissue mass, but this was not marked.

Because of the presence of the nasopharyngeal mass, a nasopharyngeal biopsy was recommended. The patient was transferred to a nearby medical center where such a biopsy was performed and a small piece of tumor tissue obtained. The pathologist reported "carcinoma, salivary gland type of the spheno-ethmoid recess." The patient was referred for supervoltage radiation therapy.

DISCUSSION

See Discussion after Case No. 221.

Case Report: CARCINOMA, SALIVARY GLAND TYPE, WITH BASAL SKULL DESTRUCTION AND CALCIFICATION.

ACKNOWLEDGMENT

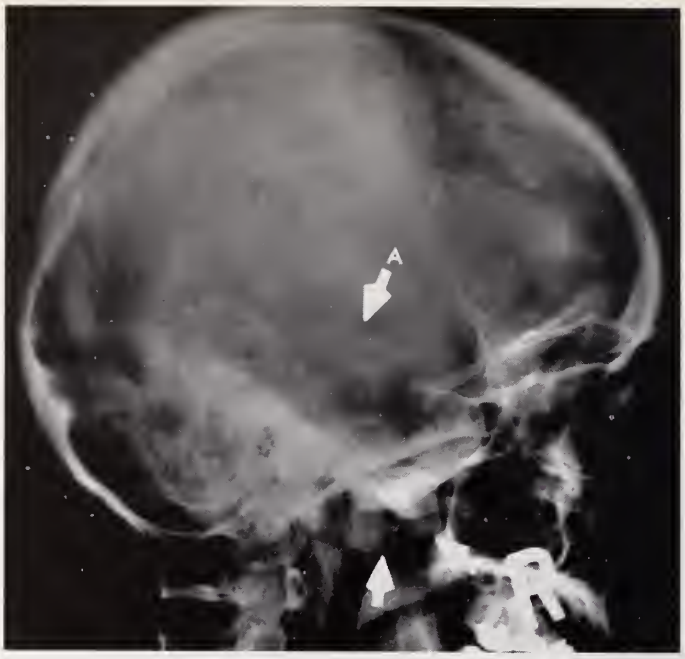
The case is presented through the courtesy of Drs. Stanley Pearl and Ralph J. Greenberg, Good Samaritan Hospital, Suffern, New York.

CASE NO. 220

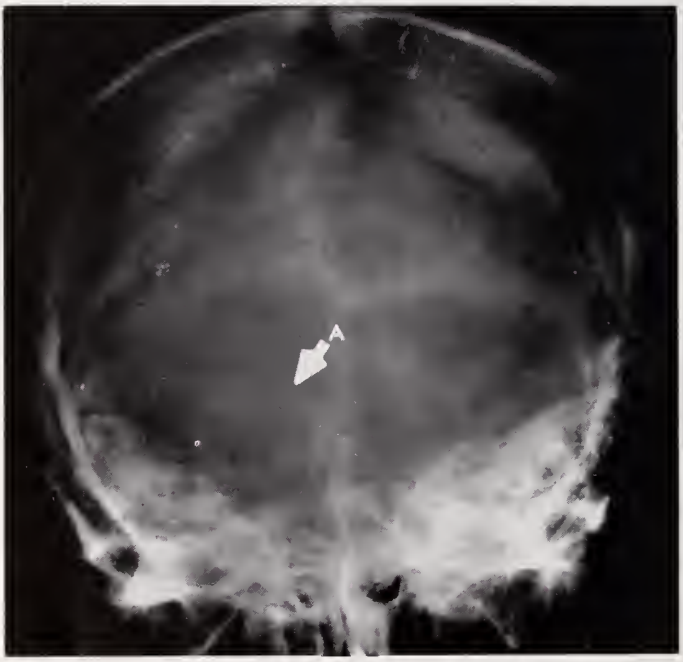
A 38 year old female was admitted with a chief complaint of right sided headache. The patient was well until three months prior to admission when she noted gradual and progressive hearing loss in the right ear. A course of antibiotic therapy yielded no improvement. Fluid was noted in the right middle ear cavity two months prior to admission and a myringotomy was performed. Shortly thereafter numbness of the right side of the face appeared and persisted. Right sided headache also developed, localized to the occipital and temporal areas; headache persisted and increased in intensity.

Physical examination revealed a prominent nodular mass on the right side of the nasopharynx. Neurologic examination revealed involvement of cranial nerves III, V, VI, and VIII, all on the right. The clinical impression was carcinoma of the nasopharynx with extension through the base of the skull.

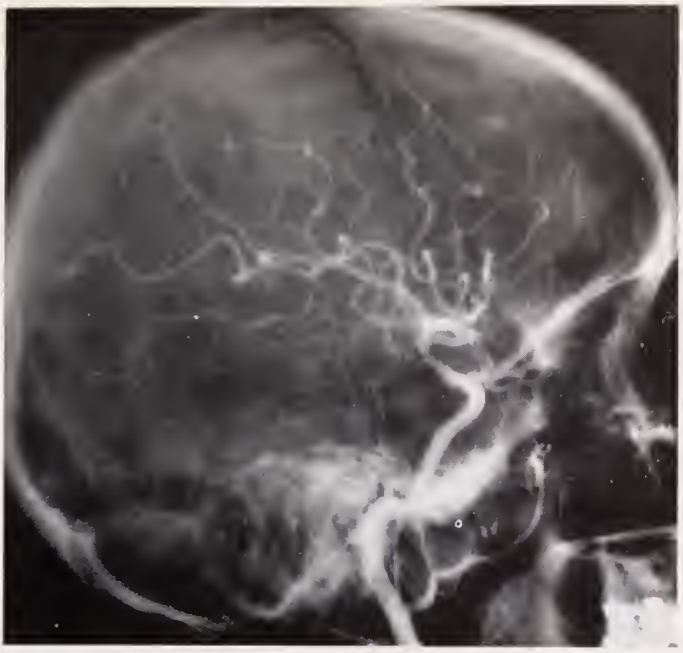
Radiographic examination of the skull (Figs. 1A, 1B) showed a mass of linear and mottled calcification in the middle cranial fossa to the right of the dorsum sellae which measured 2.5 cm in diameter. The sphenoid sinus was clouded and the floor of the sinus depressed. A soft tissue mass projected into the nasopharynx from the base of the brain. Right cerebral angiography (Figs.



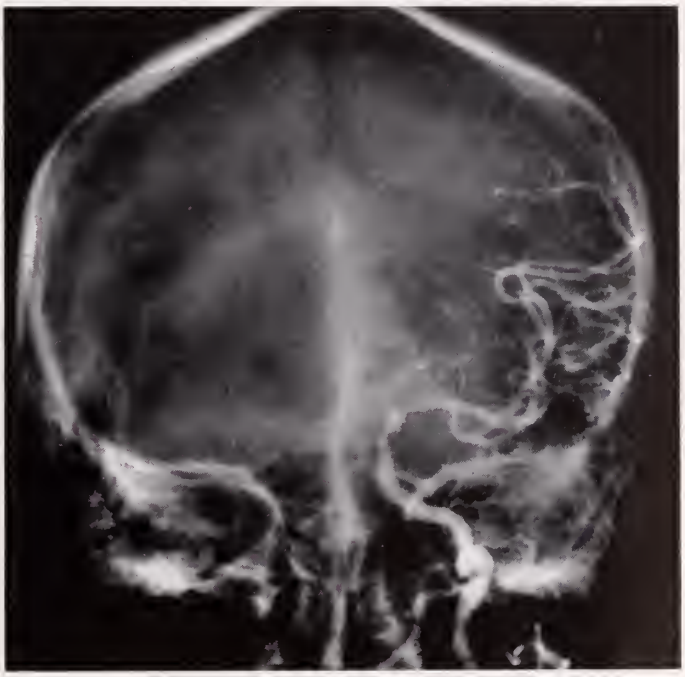
Case 220, Fig. 1A. Lateral radiograph of the skull shows a 2.5 cm mass of linear and mottled calcification lying just above the level of the dorsum sellae (arrow A). The sphenoid sinus is clouded and the floor of the sinus is depressed. A soft tissue mass is seen in the posterior portion of the nasopharynx (along arrows).



Case 220, Fig. 1B. Occipital radiograph of the skull shows the calcification to the right of the midline (arrow A).



Case 220, Fig. 2A. Lateral view during right cerebral angiogram shows elevation and straightening of the carotid siphon. Vascularity is seen along the anterior portion of the nasopharyngeal soft tissue mass but this is not marked.



Case 220, Fig. 2B. Frontal view during right cerebral angiogram shows elevation and straightening of the carotid siphon and elevation of the first portion of the middle cerebral artery.

2A, 2B) revealed elevation and straightening of the carotid siphon and the first portion of the middle cerebral artery. There was some vascularity along the anterior margin of the nasopharyngeal soft tissue mass but this was not marked.

A biopsy of the nasopharyngeal mass was performed under endotracheal anesthesia. The pathological report described multiple fragments of nasopharyngeal mucosa and bone infiltrated by chordoma. The patient was referred for supervoltage radiation therapy.

DISCUSSION

See Discussion after Case No. 221.

Case Report: Spheno-occipital chordoma with intracranial calcification and nasopharyngeal extension.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Max L. Som.

CASE NO. 221

A 55 year old male was admitted to the hospital because of diplopia. Four months prior to admission the patient noted the sudden onset of double vision while driving his automobile. He wore a patch over one eye and vision gradually returned to normal over a period of weeks. One week prior to admission double vision recurred and persisted.

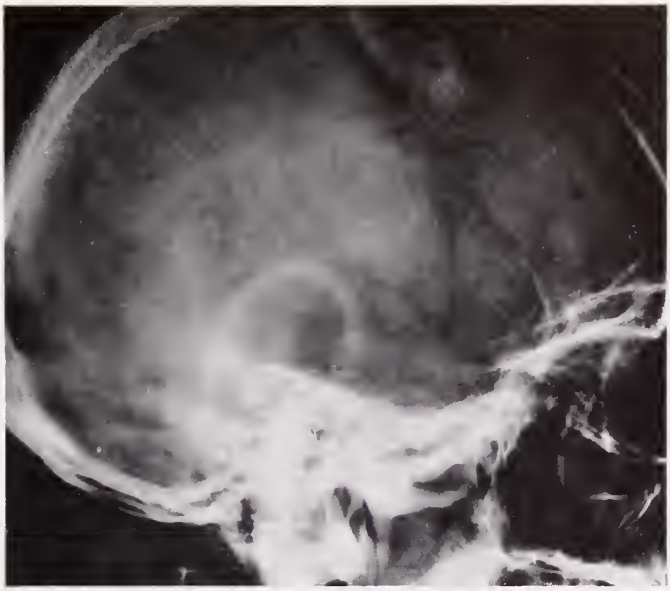
Physical examination showed slight weakness of some of the extra-ocular movements but was otherwise within normal limits. A tension test was equivocal. The initial clinical impression, however, was that of myasthenia gravis.

Radiographic examination of the skull showed complete destruction of the sella turcica and sphenoid sinus (Fig. 1). No large soft tissue mass was seen projecting into the nasopharynx. Pneumoencephalography confirmed the presence of a very large lesion at the base of the brain in relation to the destroyed sella turcica. Cerebral angiography (Fig. 2) showed marked vascularity in the region of the destroyed sella and sphenoid sinus with the appearance of a tumor stain. The stain extended to the posterior portion of the nasopharynx despite the fact that no large nasopharyngeal mass was present.

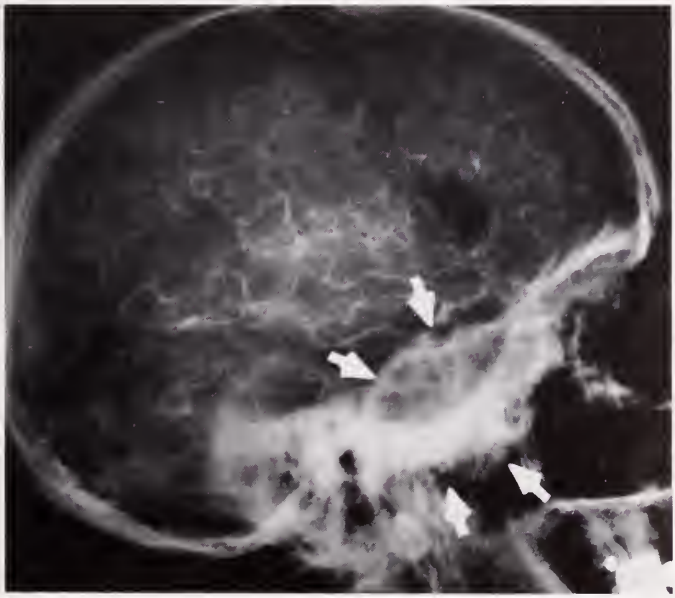
A trans-sphenoidal biopsy of the tumor was performed under endotrocheal anesthesia. Histologic examination of the specimen revealed metastatic hypernephroma. The primary tumor and the metastatic deposits were confirmed on subsequent postmortem examination.

DISCUSSION

Case Nos. 219, 220, and 221 are discussed together and represent examples of massive destruction at the base of the skull due to malignant neoplasms. Case No. 220, chordoma, is a lesion which is not uncommon in the spheno-occipital location. Calcifications in such a tumor occur but this is the exception rather than the rule. Windeyer's Case V is an excellent example in the literature which exhibited a mass of dense mottled calcification in the region of the sella turcica (1). Despite the fact that it arises from notochordal elements which are midline



Case 221, Fig. 1. Lateral view of the skull shows complete destruction of the sella turcica and the sphenoid sinus. No remarkable soft tissue mass can be seen projecting into the nasopharynx.



Case 221, Fig. 2. Lateral view of the skull during cerebral angiography shows marked vascularity in the region of the destroyed sella and sphenoid sinus (between arrows). The appearance is that of a tumor stain. The stain extends to the posterior portion of the nasopharynx but no large mass bulges into the air shadow of the nasopharynx.

in location, chordoma need not be a symmetrical midline lesion. The bulk of the mass in Case No. 220 was in the right middle cranial fossa; Windeyer's Case I was similar (1). Extension forward to produce a nasopharyngeal soft tissue mass is also quite characteristic and in fact the entire tumor may be nasopharyngeal in location. The tumor is relatively avascular as demonstrated by angiography.

Case No. 219, carcinoma of salivary gland type, is almost identical in its location and extent to Case No. 220. It must be pointed out, however, that the diagnosis in this case has been advanced on the basis of a small biopsy and some reservation about its accuracy must be held. Indeed, from the radiographic viewpoint, one would favor the diagnosis of chordoma in view of the location, size, and type of calcification. Furthermore, calcification in a salivary gland tumor is apparently quite rare. Pattinson found none in the literature and only one in his large series, his Case No. 8 (2). (This case also was diagnosed on a basis of biopsy and chordoma might be considered a possibility here as well.)

Case No. 221 again emphasizes the protean manifestations of renal carcinoma and the literature is replete with references to unusual modes of presentation of this disease. The tendency to vascularity of this neoplasm should be noted; a classical tumor stain was noted angiographically.

The list of diagnostic possibilities of a destructive lesion of the sella and the base of the brain is extensive. With the presence of calcifications in the lesion, one should consider in addition to chordoma, a chondromatous tumor, craniopharyngioma, meningioma and aneurysm.

Case Report: Metastatic hypernephroma with destruction of the base of the skull.

ACKNOWLEDGMENT

This case is presented through the courtesy of Dr. Max L. Som.

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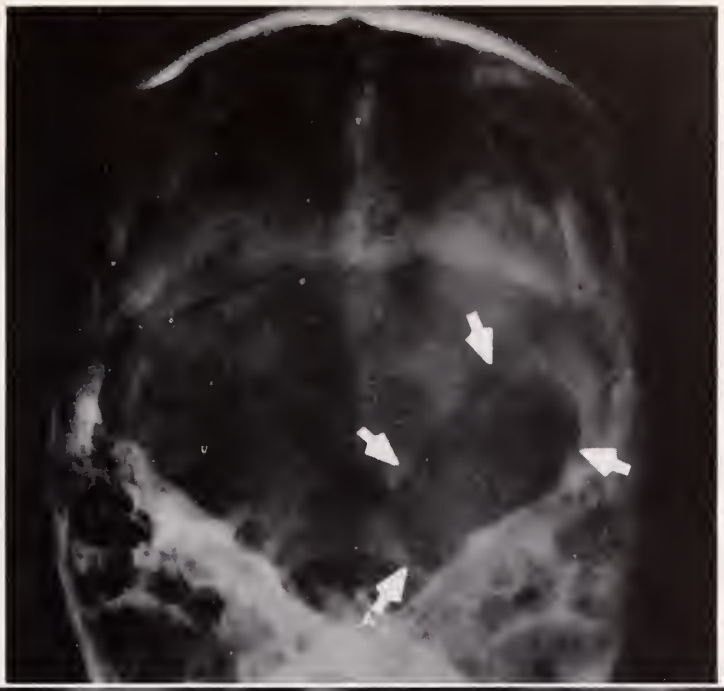
2. Pattinson, J. N.: Mucous Gland Tumors of the Nose and Throat: Radiological Appearances. Clin. Radiol., 12: 251, 1961.

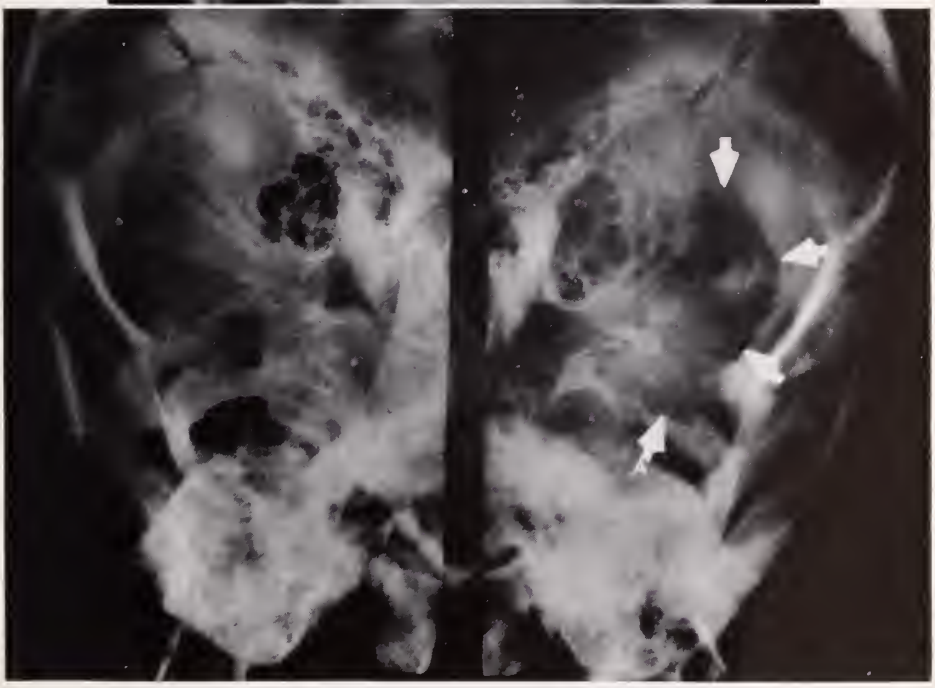
CASE NO. 222

A 21 year old female was admitted to the hospital because of tinnitus and a pressure sensation in the left ear. She complained of occasional mild pain in the

Case 222, Fig. 1A. Towne's view of the skull reveals a sharply delineated, large scalloped destructive process occupying the left occipital bone inferiorly and medially; it extends along the edge of the foramen magnum (along arrows). There is no surrounding sclerosis. Increased lucency of the petrous apex is also noted suggesting bone destruction. The arch of the atlas is seen through the foramen magnum and the left side of its neural arch appears to be partially destroyed (arrow A).

Case 222, Fig. 1B. Lateral-oblique views of both occipital regions for purposes of comparison reveal that the right occipital region and the right arch of the atlas are normal. On the left side, the large defect in the occipital bone is again well demonstrated (along arrows). The extension into the atlas is apparent (arrow A).





occipital region and upper neck. There was no hearing defect or vertigo. Physical examination was negative except for the findings in the left ear. The inferior third of the tympanic membrane had a blue discoloration and was noted to have a yellowish bulge posteriorly in its superior aspect. Audiometric testing revealed a mild conductive deafness in the left ear.

Radiologic examination of the skull revealed a large, sharply outlined, scalloped area of bone destruction in the left occipital bone inferiomedially, extending downward to involve the left side of the arch of the atlas (Figs. 1A, 1B). There was no surrounding bony sclerosis. Decreased lucency of the apex of the left petrous pyramid was also noted, suggesting some degree of bony destruction in this region. Tomographic studies of the petrous bone revealed a sharply outlined irregular bony defect in the region of the jugular bulb. An open biopsy of the occipital bone was performed and a grape-sized nodule was encountered and subtotally resected; this was firm and not unusually vascular. Microscopic examination revealed fragments of bone and muscle invaded by giant cell tumor (osteoclastoma). A course of Cobalt-60 radiotherapy was then given to the left occipital region. At the end of the treatment there was improvement in the tinnitus, headaches and the conduction deafness were less pronounced.

DISCUSSION

Giant cell tumors are benign neoplasms of potential malignant nature. They occur primarily in long bones, especially in the lower extremity near the knee joint. Only rarely are they localized within the bones of the skull (1). Jaffe claims that when they are located in the skull, the involved bone is always the site of previous Paget's disease or fibrous dysplasia (2). Geschickter and Copeland suggest that osteoclastomas of the skull should be restricted to those parts of the skull which develop from the chondrocranium. As of 1960, only ten well-substantiated cases of giant cell tumors of the skull had appeared in the literature (3). In the differential diagnosis of destructive lesions in this portion of the skull, one must consider benign osteoblastoma, glomus jugulare tumor and metastatic tumors. Benign osteoblastomas are tumors which may be located in flat as well as long bones and may closely resemble giant cell tumors histologically. In fact, Jaffe maintains that most of the so-called giant cells tumors of the skull are actually benign osteoblastomas. However, radiologically, areas of stippled calcification within the tumor are usually easily identified. These lesions are rare in the skull and it would be quite unusual for them to extend across the base of the skull and involve the first cervical vertebra. Clinically, the present case conforms closely to the symptom complex usually associated with glomus jugulare tumors. Radiologically, these latter tumors also present as sharply demarcated areas of bone destruction but their localization is specifically limited to the petrous apex and the immediately surrounding structures. They never extend as far as the foramen magnum as in the present case. Metastatic tumors may occur any place within the skull but for a tumor the size of the one described, one would expect considerably more symptoms of increased intracranial pressure within the posterior fossa as well as a soft tissue component within the scalp.

Because of the large size of the tumor and its strategic location, extirpative surgery was deemed impossible and Cobalt-60 radiotherapy was given in an attempt to prevent further extension and if possible to reduce the size of the lesion. The post-treatment follow-up period is yet too short to evaluate the efficacy of this therapy.

Case Report: Giant cell tumor (osteoclastoma) of occipital bone and atlas.

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CASE NO. 223

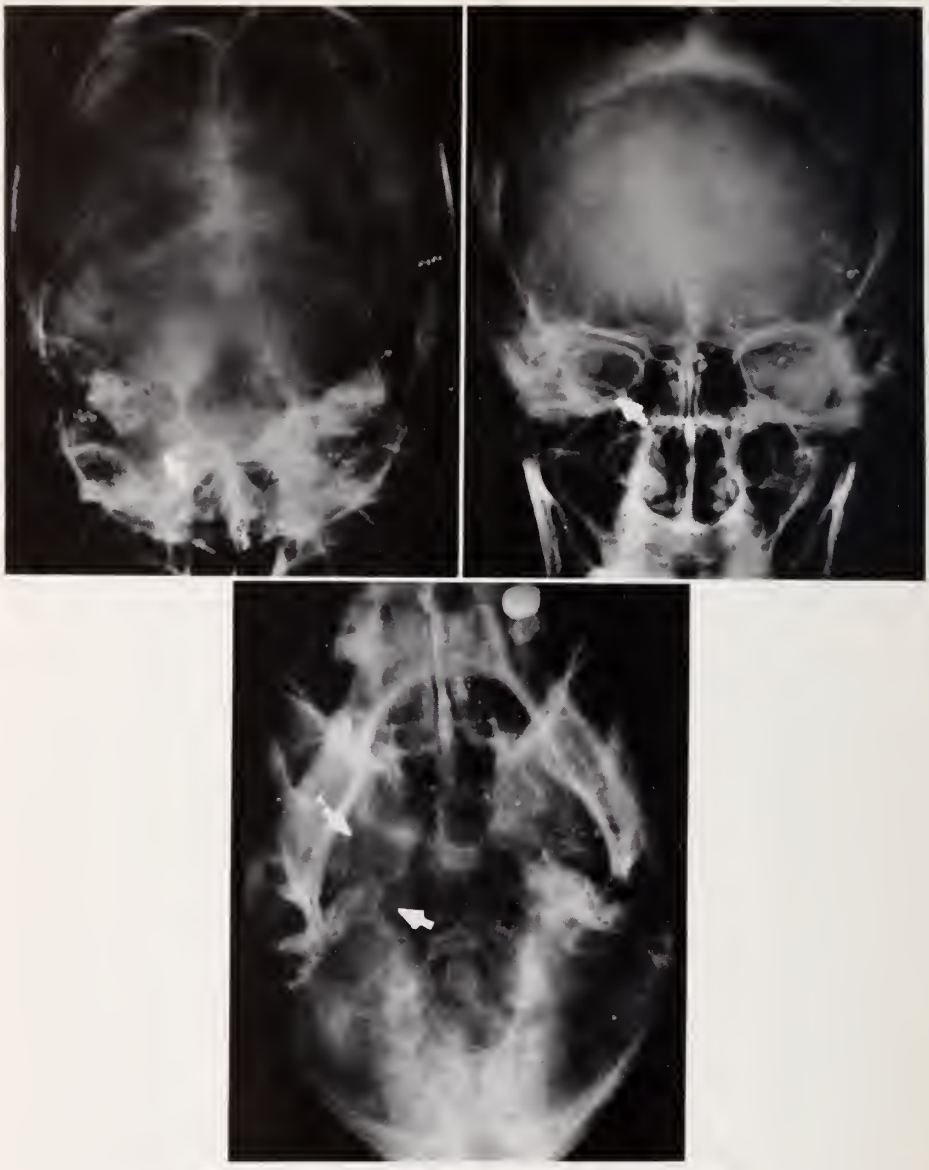
A 56 year old female presented with a two and one half year history of tinnitus in the right ear and mild hoarseness of a slowly progressive nature. Six months before her present hospitalization, she became aware of decreased hearing and pain in the right ear. Within the last month, she also noticed the onset of weakness on the right side of the face and right eyelid. Recently the hearing deficit and tinnitus became much more pronounced. Positive physical findings were limited to the head and neck. A solid, whitish mass was seen bulging the lower half of the right eardrum. There was total deafness on that side. Marked weakness of the entire musculature of the right side of the face was apparent. There was fibrillation of the muscles of the anterior pillar of the right fauces and the right side of the tongue, associated with hemiatrophy. There was weakness and atrophy of the right sternoclidomastoid and trapezius muscles. The right vocal chord was noted to be paralyzed.

Radiologic examination of the skull with special studies of the petrous bones revealed a destructive lesion at the base of the petrous pyramid on the right side in the region of the jugular bulb (Figs. 1A, 1B). This area of bone destruction involved the internal auditory meatus medially and extended forward into the middle cranial fossa to erode the foramen ovale (Fig. 1C). Posteriorly, it extended into the medial aspect of the posterior cranial fossa.

A tympanomeatal flap was then raised and a reddish-purple lobulated vascular tumor was visualized within the middle ear. Because of its extent, only biopsies were taken without attempting to remove it surgically. Histologic examination was typical of a glomus jugulare tumor (chemodectoma). A course of rotational Cobalt-60 therapy was then instituted. Marked improvement in the tinnitus and hearing defect was soon apparent and the patient regained considerable strength in the muscles on the right side of the face, neck and shoulder.

DISCUSSION

Since the first case of glomus jugulare tumor was described by Rosenwasser in 1945 (1), approximately 250 well-substantiated cases have appeared in the literature (2). These tumors arise from chemoreceptive tissue located in the jug-



Case 223, Fig. 1A. Towne's projection of the skull reveals an area of bone destruction involving the tip of the petrous apex on the right side (arrow)

Case 223, Fig. 1B. In the anteroposterior view of the skull, the destructive process is well seen and is noted to involve the internal auditory meatus and the medial aspect of the internal auditory canal on the right (arrow).

Case 223, Fig. 1C. In the base view of the skull, the destructive process is noted to involve the region of the right jugular bulb (arrow). The foramen ovale is also noted to be widened and scalloped in outline indicating extension of the lesion into the middle cranial fossa (arrow A).

ular bulb. The structures were first described by Guild in 1941 (3). The glomus jugulare tumors are locally invasive and are usually very slowly progressive. Typically, the patient is middle-aged and complains of tinnitus, hearing loss, and often has symptoms referable to involvement of the cranial nerves, aside from the acoustic nerve—VII, IX, X, XI and XII. Radiologically, there is evidence of varying degree of erosion of the petrous apex in the region of the jugular bulb. Often, there is coexistent sclerosis of the mastoid cells. These features are best visualized in the Towne's view of the skull and the Stenver's projection of the petrous bone. Laminographic studies help delineate the extent of the destruction. Glomus jugulare tumors are usually radiosensitive.

Case Report: Glomus jugulare tumor—chemodectoma.

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